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

Updates effective 09/01/2022

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) includes 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 Washington State Rx Services 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 Washington State Rx Services 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 Washington State Rx Services at 1-888-361-1611 (TRS: 711)
- Refer to the UMP Preferred Drug List by visiting hca.wa.gov/ump-pdl.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP141

Description
Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist that works by suppressing bile acid synthesis and increasing bile acid transport out of the hepatocytes, thus reducing overall hepatic exposure to toxic levels of bile acids.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>obeticholic acid</td>
<td>5 mg tablets</td>
<td>Primary Biliary Cholangitis (PBC)</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>(Ocaliva)</td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Obeticholic acid (Ocaliva) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; AND
   B. A diagnosis of Primary Biliary Cholangitis (PBC) [i.e. primary biliary cirrhosis]; AND
      1. Diagnosis confirmed by TWO of the following:
         i. Alkalaine phosphate (e.g. ALP) level at least 1.5 times the upper limit of normal
         ii. Positive antimitochondrial antibodies (AMA) test
         iii. Histopathologic evidence (i.e. nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); AND
      2. Treatment with ursodeoxycholic acid (e.g. Urso, Ursodiol) has been ineffective, contraindicated, or not tolerated; AND
         i. Inadequate response is defined as an alkaline phosphate level greater than 1.67 times the upper limit of normal after one year of treatment with ursodeoxycholic acid; AND
      3. Member has compensated liver disease (Child-Pugh A).

II. Obeticholic acid (Ocaliva) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-alcoholic steatohepatitis (NASH)
   B. Non-alcoholic fatty liver disease (NAFLD)
C. Familial partial lipodystrophy  
D. 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. Member has a diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; **AND**
   
   A. Member has compensated liver disease (Child-Pugh A); **AND**

IV. Member has exhibited improvement or stability of disease symptoms (e.g. reduction of pruritus, reduced fatigue, or decrease in alkaline phosphate levels)

Supporting Evidence

I. Obeticholic acid (Ocaliva) is FDA-approved for the treatment of primary biliary cholangitis (PBC) when used in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA; or, as monotherapy in adults unable to tolerate UDCA.  

II. Per the American Association for the Study of Liver Diseases (AASLD) guidelines, UDCA at a dose of 13 to 15 mg/kg/day is the first-line therapy for PBC.  

III. Treatment response in PBC is monitored using liver biochemical values - specifically, serum ALP and total bilirubin. Improvements in liver tests are typically seen within a few weeks, with the majority of liver test improvements occurring within 6 to 9 months. About 20% of patients will have normalization of liver biochemistries after two years.  

IV. Per guidelines, the benefit of obeticholic acid (Ocaliva) in patients with decompensated liver disease is unestablished. In September 2017, the FDA issued a warning regarding inappropriate dosing of obeticholic acid (Ocaliva) in patients with moderate to severe liver impairment (Child-Pugh-Turcotte B and C), which was associated with worsening PBC and death. Therefore, the use of obeticholic acid (Ocaliva) in patients with decompensated PBC is not recommended.

Investigational or Not Medically Necessary Uses

I. Obeticholic acid (Ocaliva) has not been sufficiently evaluated in the following settings:  
   
   A. Non-alcoholic steatohepatitis (NASH)  
      
      1. Obeticholic acid (Ocaliva) is being studied in an ongoing clinical trial that enrolled 2,480 participants. A total of 931 patients with stage F2–F3 fibrosis were included in the primary analysis [311 in the placebo group, 312 in the obeticholic acid (Ocaliva) 10 mg group, and 308 in the obeticholic acid (Ocaliva) 25 mg group]. An interim analysis was done after a minimum of 750 randomized patients with fibrosis stages F2 or F3 reached their actual or planned month-18 visit.  
         o The primary endpoint of fibrosis improvement by at least one stage with no worsening of NASH was met by 37 (12%) patients in the placebo group, 55 (18%) patients in the obeticholic acid (Ocaliva) 10 mg group (p=0.045
vs placebo), and 71 (23%) patients in the obeticholic acid (Ocaliva) 25 mg group (p=0.0002 vs placebo).

- The primary endpoint of NASH resolution (based on no hepatocellular ballooning and no residual lobular inflammation) with no worsening of fibrosis did not meet statistical significance in the intent-to-treat population (25 [8%] patients in the placebo group vs 35 [11%] in the obeticholic acid (Ocaliva) 10 mg group [p=0.18] or 36 [12%] in the obeticholic acid (Ocaliva) 25 mg group [p=0.13]).
- Treatment-emergent adverse events occurred in 548 (83%) patients in the placebo group, 579 (89%) in the obeticholic acid (Ocaliva) 10 mg group, and 601 (91%) in the obeticholic acid (Ocaliva) 25 mg group.
- Pruritus was the most common adverse event and was seen in 123 (19%) patients in placebo group, 183 (28%) patients in the obeticholic acid (Ocaliva) 10 mg group, and 336 (51%) patients in the obeticholic acid (Ocaliva) 25 mg group.
- The end-of-study analysis will evaluate the effect of obeticholic acid (Ocaliva) on clinical outcomes (including progression to cirrhosis and all-cause mortality) and the long-term safety of obeticholic acid and will be completed once approximately 291 adjudicated clinical outcome events occur. Patients are expected to have a minimum follow-up time of approximately 4 years.

2. According to the practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association first line treatment for NASH is weight loss as it generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.

3. Based on the data reviewed to date, the predicted benefit of obeticholic acid (Ocaliva) based on a surrogate histopathologic endpoint remains uncertain and does not sufficiently outweigh the potential risks for the treatment of patients with liver fibrosis due to NASH. Additional efficacy and safety data are needed to support its use in NASH.

B. Non-alcoholic fatty liver disease (NAFLD)
C. Familial partial lipodystrophy
D. Obesity

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added supporting evidence for the investigational use in NASH</td>
<td>07/2020</td>
</tr>
<tr>
<td>Prior authorization criteria transitioned to policy format. Updated initial and renewal durations. Addition of specialist requirements. Addition of confirmed diagnosis and Child Pugh A classification. Further clarification of characteristics of inadequate response to ursodeoxycholic acid. Addition of renewal criteria.</td>
<td>12/2019</td>
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<tr>
<td>Policy created</td>
<td>06/2016</td>
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</table>
octreotide (Sandostatin®, Bynfezia Pen™, Mycapssa®)  
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>octreotide acetate (generic, Sandostatin)</td>
<td>50 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td>90 ampules, vials, syringes/30 days</td>
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<tr>
<td></td>
<td>100 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td>9 vials/30 days</td>
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<tr>
<td></td>
<td>500 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td>2 vials/30 days</td>
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<tr>
<td></td>
<td>1000mcg/5mL (200 mcg/mL) vial</td>
<td>Acromegaly</td>
<td>112 capsules/28 days</td>
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<td>octreotide acetate (Bynfezia Pen)</td>
<td>7000mcg/2.8mL (2500 mcg/mL) prefilled injection pen</td>
<td>Acromegaly</td>
<td>2 pens/30 days</td>
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<td>octreotide acetate (Mycapssa)</td>
<td>20 mg capsule</td>
<td>Acromegaly</td>
<td>112 capsules/28 days</td>
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</tbody>
</table>

Provider Administered Agents*  

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.

September 01, 2022
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<table>
<thead>
<tr>
<th>octreotide acetate, mi-spheres (Sandostatin LAR)</th>
<th>10 mg vial</th>
<th>Acromegaly; Metastatic carcinoid tumor; Vasoactive intestinal peptide tumor (VIPoma)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg vial</td>
<td>30 mg vial</td>
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</table>

*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 **investigational**. 

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September 01, 2022
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.

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 IGF-1 ≤ 1.0 x 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 ≤ 1.0 x 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

2. Melmed, S. Treatment of acromegaly. In: UpToDate. Martin, KA (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Bynfezia Pen to policy with requirement for inadequate response to generic 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.</td>
<td>9/2020</td>
</tr>
<tr>
<td>Transitioned to policy format and updated the following:</td>
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<tr>
<td>• Added age requirement of 18 years or older</td>
<td>12/2019</td>
</tr>
<tr>
<td>• For octreotide (Sandostatin), added requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated</td>
<td></td>
</tr>
<tr>
<td>• Removed octreotide (Sandostatin LAR) from the policy as it is excluded from coverage under the pharmacy benefit</td>
<td></td>
</tr>
<tr>
<td>Previous review</td>
<td>10/2017</td>
</tr>
<tr>
<td>Criteria created</td>
<td>10/2016</td>
</tr>
</tbody>
</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP243

Description
Odevixibat (Bylvay™) is an orally administered reversible ileal bile acid transporter (IBAT) inhibitor.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>odevixibat (Bylvay)</td>
<td>200 mcg pellets</td>
<td>Pruritis in patients three months of age and older with progressive familial intrahepatic cholestasis (PFIC)</td>
<td>Monthly quantity to allow for a maximum of 120 mcg/kg per day</td>
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<tr>
<td></td>
<td>400 mcg pellets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>600 mcg capsules</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1200 mcg capsules</td>
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</table>

Initial Evaluation

I. **Odevixibat (Bylvay) may be considered medically necessary when the following criteria are met:**
   A. Member is three months of age or older; **AND**
   B. Documentation of member’s weight, measured within past three months, is provided; **AND**
   C. Medication is prescribed by, or in consultation with a hepatologist or gastroenterologist; **AND**
   D. A diagnosis of **progressive familial cholestasis (PFIC)** when the following are met:
      1. Other causes of cholestasis have been ruled out (e.g., drug toxicity, hepatitis A, sclerosing cholangitis, Alagille syndrome); **AND**
      2. Diagnosis is confirmed by a molecular genetic test; **AND**
      3. Member does not have PFIC type 2 with ABCB11 variant resulting in nonfunctional or absent bile salt export pump protein (BSEP-3) as confirmed by a molecular generic test; **AND**
      4. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**
      5. Provider attestation of presence of moderate to severe pruritis; **AND**
      6. Treatment with **ALL** the following has been ineffective, contraindicated, or not tolerated:
         i. Ursodiol; **AND**
         ii. Bile acid sequestrant (e.g., cholestyramine, colesvelam); **AND**
         iii. Rifampin; **AND**
         iv. Opioid antagonist (e.g., naltrexone); **AND**
         v. Serotonin reuptake inhibitor (e.g., sertraline)
I. Odevixibat (Bylvay) is considered **investigational** when used for all other conditions, including but not limited to:
   - A. Benign recurrent intrahepatic cholestasis (BRIC) 1 and 2
   - B. Alagille syndrome
   - C. Primary sclerosing cholangitis
   - D. Biliary Atresia

**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; **AND**

VI. Member has not progressed to decompensated cirrhosis or experience hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

**Supporting Evidence**

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 \textit{ATP8B1} gene. This gene is also expressed in small intestine, kidney, and pancreas, which explains certain extrahepatic manifestations (e.g., sensorineural deafness). PFIC2 occurs due to mutations on the \textit{ABCB11} gene and PFIC3 is due to reduced expression of multidrug resistance MDR3, which is encoded by \textit{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. 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 transplant. 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.

III. 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.
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.

IV. 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.

V. Odevixibat (Bylvay) is 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) to inhibit the reabsorption of bile salts in the gastrointestinal tract cannot be expected.

VI. 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. 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) is not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.

VII. Odevixibat (Bylvay) was not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Odevixibat (Bylvay) 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.

VIII. 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 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. Therefore, the value of odevixibat (Bylvay) in patients with mild pruritis has not been established and the drug may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

IX. 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.
• **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 pruritus 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 pruritus. Pruritus 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 pruritus associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritus associated with cholestasis. Despite 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 pruritus 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 pruritus 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 pruritus in pediatric patients with PFIC by EASL guidelines. Additionally, there are various reports in literature showing positive results on pruritus 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 treatment of pruritus in patients with cholestasis associated with chronic liver diseases (Khurana, 2006).

• **Opioid antagonist** - naltrexone is recommended for the treatment of pruritus 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 pruritus (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).

• **Sertraline** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritus. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritus due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritus related to PFIC and Alagille syndrome (Thebaut, 2017).
X. 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 pruritus assessments (PPAs) as measured by the single-item observer-reported outcome instrument (ObsRo). 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.

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Placebo (n=20)</th>
<th>Odevixibat 40 µg/kg/day (n=23)</th>
<th>Odevixibat 120 µg/kg/day (n=19)</th>
<th>All odevixibat (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean (SE) proportion of PPAs, %</td>
<td>30.1</td>
<td>58.3</td>
<td>51.8</td>
<td>55.1</td>
</tr>
<tr>
<td>LS mean Δ, (95% CI), [p-value]</td>
<td>28.2 (9.8-46.6), [0.003]</td>
<td>21.7 (1.9-41.5), [0.033]</td>
<td>25.0 (8.5-41.5), [0.004]</td>
<td></td>
</tr>
<tr>
<td>Patients with sBA response, %</td>
<td>0</td>
<td>43.5</td>
<td>21.1</td>
<td>33.3</td>
</tr>
<tr>
<td>Proportion Δ in sBA, (95% CI), [p-value]</td>
<td>0.435 (0.22-0.66), [0.001]</td>
<td>0.211 (0.02-0.46), [0.035]</td>
<td>0.333 (0.09-0.050), [0.003]</td>
<td></td>
</tr>
</tbody>
</table>

XI. The safety data for odevixibat (Bylvay) is available for 69 patients. In PEDFIC1, adverse events (AEs) reported in ≥ 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 odevixibat (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.

Investigational or Not Medically Necessary Uses

I. Odevixibat (Bylvay) has 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. Alagille syndrome, primary sclerosing cholangitis, biliary atresia
      i. Odevixibat (Bylvay) was studied in one Phase 2, open-label, single-arm study in pediatric patients with diagnosis of pruritis due to cholestatic disease (including but not limited to PFIC, Alagille syndrome, primary sclerosing cholangitis, and biliary atresia). Most patients experienced reductions in serum bile acid levels
which correlated with improvements in pruritus and sleep disturbance scores. The quality of evidence is low at this time and phase 3 randomized controlled studies are warranted to confirm treatment benefit.

ii. Phase 3, double-blind, randomized controlled trials in patients with biliary atresia (NCT04336722) and in patients with Alagille Syndrome (NCT04674761) are currently under way.

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. Table 1: Recommended Dosage for 40mcg/kg/day

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Total Daily Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4 and below</td>
<td>200</td>
</tr>
<tr>
<td>7.5 to 12.4</td>
<td>400</td>
</tr>
<tr>
<td>12.5 to 17.4</td>
<td>600</td>
</tr>
<tr>
<td>17.5 to 25.4</td>
<td>800</td>
</tr>
<tr>
<td>25.5 to 35.4</td>
<td>1200</td>
</tr>
<tr>
<td>35.5 to 45.4</td>
<td>1600</td>
</tr>
<tr>
<td>55.5 and above</td>
<td>2400</td>
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References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>11/2021</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>olaparib</td>
<td>Breast cancer, early, high-risk, HER2-negative, gBCRAm, adjuvant therapy;</td>
<td>100 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer, advanced gBRCAm;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer, first-line maintenance therapy for gBRCAm or somatic BRCAm-</td>
<td>150 mg tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mutated (sBRCAm) or homologous recombination deficient-positive (HRD);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer, recurrent (maintenance therapy);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic cancer, first-line therapy for gBRCAm-mutated, metastatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adenocarcinoma;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate cancer, metastatic castration-resistant, homologous recombination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>repair (HRR) gene-mutated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, Recurrent Maintenance; AND**
         i. Diagnosis of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; **AND**
         ii. Has completed at least **TWO** prior platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimens; **AND**
         iii. The tumor is considered to be platinum-sensitive (i.e., the patient is responsive to their most recent platinum-based regimen, as defined by complete or partial response for more than 6 months); **AND**
         iv. Provider attests, with supporting documentation, that member’s recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimen; **AND**
         v. Medication will not be used in combination with other anti-cancer agents; **OR**
      2. **Ovarian cancer, First-line Maintenance; AND**
         i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) of gBRCAm OR sBRCAm; **AND**
         ii. Has **not** received bevacizumab in prior treatment; **OR**
            a. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gHRDm (homologous recombination deficient-positive mutation); **AND**
            b. Member has had a positive response to prior bevacizumab treatment and bevacizumab will be continued; **AND**
         iii. Diagnosis of advanced (stage ≥III) epithelial ovarian, fallopian tube, or primary peritoneal cancer; **AND**
         iv. Has completed at least **ONE** prior platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
         v. The tumor is considered to be platinum-sensitive (i.e., the patient is responsive to their most recent platinum-based regimen, as defined by a complete or partial response for more than 6 months); **AND**
         vi. Provider attest with supporting documentation that member’s epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimen; **AND**
         vii. Medication will not be used in combination with other anti-cancer agents; **OR**
      3. **Ovarian cancer, Advanced; AND**

i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm OR sBRCAm; **AND**

ii. Diagnosis of advanced (stage ≥III) epithelial ovarian, fallopian, or primary peritoneal cancer; **AND**

iii. Has had progression of disease following three or more prior lines of chemotherapy; **AND**

iv. Medication will not be used in combination with other anti-cancer agents; **OR**

4. 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) BRCA mutations (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 breast cancer; **AND**
      a. Has received prior treatment with both an anthracycline (e.g., doxorubicin) AND a taxane (e.g., paclitaxel) in the neoadjuvant, adjuvant, or metastatic setting; **AND**
      b. Has not received more than two prior chemotherapy regimens in the metastatic setting; **AND**
      c. Has progression of disease on at least one prior endocrine therapy in the adjuvant or metastatic setting; **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**

5. 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**
   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

6. Prostate cancer, Metastatic castration-resistant; AND
   i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in at least one of the following HRR genes: ATM, BRCA1, BRCA2; AND
   ii. Has progressed on prior enzalutamide or abiraterone treatment; AND
   iii. Member has had a prior bilateral orchiectomy; OR
      a. Used in combination with luteinizing-hormone-releasing hormone analog therapy (e.g. leuprolide (Eligard, Lupron), histrelin (Vantas))

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)
   F. Use after disease progression on or after prior PARP inhibitor therapy
   G. Use in combination with other anti-cancer agents

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]); 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 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 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks. There can be some flexibility within reason but use clinical judgement and patient specific factors when assessing this criterion to ensure this is falling within the maintenance treatment timeframe vs subsequent therapy.

- 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.

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.

- 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 contraindi cated) and a taxane. Approximately 70% of patients had received treatment in the metastatic setting; however, patients had received no more than two previous chemotherapy regimens for metastatic disease. More than two therapies in other settings (e.g., neoadjuvant, adjuvant) did not apply to this criterion. 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 the olaparib and placebo 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, quality of life was based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, there was no significant between-group differences in health-related quality of life, as indicated by the overall change from baseline in the global quality-of-life
score (on a 100-point scale, with higher scores indicating better quality of life (between-group difference, −2.47 points; 95% CI, −7.27 to 2.33)).

- As it currently stands, treatment with olaparib (Lynparza) in the setting of metastatic gBRCam pancreatic cancer showed no difference in overall survival (OS) and quality of life (QoL) when compared to placebo. Therefore, limited exception should be granted to those who do not meet the criteria for metastatic, gBRCam pancreatic cancer as stated in this policy.

- The preferred systemic regimens for metastatic, gBRCam pancreatic cancer include:
  i. FOLFIRINOX or modified FOLFIRINOX ± subsequent chemoradiation
  ii. Gemcitabine + albumin-bound paclitaxel ± 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 orchidectomy or were using luteinizing-hormone-releasing hormone 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, overall survival (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.

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 has 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 has 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 has 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 progression of disease on another PARP inhibitor.

V. Metastatic castration-resistant prostate cancer with other tumor mutations (including BRD1, 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 (BRD1, 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.

* 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


Washington State Rx Services is administered by modasHEALTH

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.

September 01, 2022
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.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Disease State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Talazoparib (Talzenna)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Niraparib (Zejula)</td>
<td>Ovarian Cancer</td>
</tr>
<tr>
<td>Rucaparib (Rubraca)</td>
<td>Ovarian Cancer</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Advanced prostate cancer</td>
</tr>
<tr>
<td></td>
<td>Advanced breast cancer in premenopausal women</td>
</tr>
<tr>
<td></td>
<td>Reduction of endometrial thickness prior to endometrial ablation</td>
</tr>
<tr>
<td></td>
<td>Gender dysphoria</td>
</tr>
<tr>
<td></td>
<td>Central Precocious Puberty (CPP)</td>
</tr>
<tr>
<td></td>
<td>Uterine leiomyoma (fibroids)</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
<tr>
<td>darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), abiraterone (Zytiga, Yonsa)</td>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>06/2022</td>
</tr>
<tr>
<td>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.</td>
<td>10/2020</td>
</tr>
<tr>
<td>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.</td>
<td>02/2020</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>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.</td>
<td>03/2019</td>
</tr>
<tr>
<td>Criteria update: Added coverage criteria for ovarian cancer maintenance and metastatic breast cancer</td>
<td>02/2018</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omacetaxine mepesuccinate (Synribo)</td>
<td>3.5 mg vial</td>
<td>Chronic or accelerated phase CML</td>
<td>Initial: 28 vials/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 14 vials/28 days</td>
</tr>
</tbody>
</table>

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 performed 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

**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Date Created</th>
<th>February 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>February 2013</td>
</tr>
<tr>
<td>Last Updated</td>
<td>December 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>12/2019</td>
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</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
</tbody>
</table>
omalizumab (Xolair®)
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>omalizumab (Xolair)</td>
<td>Allergic asthma**</td>
<td>75 mg/0.5mL prefilled syringe</td>
<td>1 syringe per 28 days</td>
</tr>
<tr>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic rhinosinusitis with nasal polyposis (CRSwNP)**</td>
<td>150 mg/mL prefilled syringe</td>
<td>1 syringe per 28 days</td>
</tr>
<tr>
<td></td>
<td>Allergic asthma**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic rhinosinusitis with nasal polyposis (CRSwNP)**</td>
<td>150 mg/mL prefilled syringe</td>
<td>1 syringe per 28 days</td>
</tr>
<tr>
<td></td>
<td>Chronic idiopathic urticaria (CIU)</td>
<td>150 mg/mL prefilled syringe</td>
<td>2 syringes per 28 days</td>
</tr>
<tr>
<td></td>
<td>Allergic asthma**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic rhinosinusitis with nasal polyposis (CRSwNP)**</td>
<td>150 mg vial*</td>
<td>1 vial per 28 days</td>
</tr>
<tr>
<td></td>
<td>Chronic idiopathic urticaria (CIU)</td>
<td>150 mg vial*</td>
<td>2 vials per 28 days</td>
</tr>
</tbody>
</table>

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, etc.); AND

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. 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. \( \geq 30 \text{ IU/mL and } \leq 700 \text{ IU/mL in members age } \geq 12 \text{ years; OR} \)
      b. \( \geq 30 \text{ IU/mL and } \leq 1300 \text{ IU/mL in members age } 6 \text{ to } <12 \text{ years; AND} \)
   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
      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 (CIU); 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. Documented baseline score from an objective clinical evaluation tool, such as: urticaria activity score (UAS7), angioedema activity score (AAS), Dermatology Life Quality Index (DLQI), Angioedema Quality of Life (AE-QoL), or Chronic Urticaria Quality of Life Questionnaire (CU-QoL); AND

v. Member had an inadequate response to a minimum (1) month trial on previous therapy of a second-generation H1-antihistamine product*; AND

vi. 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; OR

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., presyncope, 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 polyposis (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
   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. Documentation of current persistent symptomatic nasal polyps despite maximal treatment with ALL of the following, unless ineffective, not tolerated, or contraindicated:
a. Intranasal corticosteroid; **AND**
b. Oral systemic corticosteroid therapy within the last 12 months; **AND**
   vi. Background intranasal corticosteroid will be continued with the use of omalizumab (Xolair), unless contraindicated.

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
   B. Esophagitis
   C. Interstitial cystitis
   D. Painful bladder syndrome
   E. Eosinophilic bronchitis
   F. Multi-food oral immunotherapy
   G. Bullous pemphigoid
   H. Peanut allergy
   I. Chronic spontaneous urticaria
   J. Solar urticaria
   K. Chronic urticaria
   L. Cholinergic urticaria
   M. Seasonal allergic rhinitis

**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, 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 (CIU)**; **AND**
      1. Member has exhibited improvement or stability of disease symptoms from baseline using objective clinical evaluation tools (e.g., urticaria activity score [UAS7], angioedema activity score [AAS], Dermatology Life Quality Index [DLQI], Angioedema Quality of Life [AE-QoL], or Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL]); **AND**
      2. Submitted current UAS7, AAS, DLQI, AE-QoL, or Cu-Q2oL was recorded within the past 30 days; **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.

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), and as chronic idiopathic urticaria in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.
   - Omalizumab (Xolair) is not FDA approved for use in the setting of systemic mastocytosis; however, it is compendia recommended.

III. Omalizumab (Xolair) prefilled syringes have been FDA approved for self-administration for the treatment of asthma in patients 6 years and older, chronic idiopathic urticaria (CIU) in patients 12 years and older, and nasal polyps in patients age 18 years 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 Xolair prefilled syringe 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 with proper technique according to the prescribed dosing regimen and Instructions for Use

IV. 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...
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.

V. **Chronic idiopathic urticaria (CIU)**

- 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.

<table>
<thead>
<tr>
<th>XOLAIR</th>
<th>XOLAIR</th>
<th>XOLAIR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>75mg</td>
<td>150mg</td>
<td>300mg</td>
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</tr>
<tr>
<td>n</td>
<td>77</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Mean Baseline Score (SD)</td>
<td>14.5 (3.6)</td>
<td>14.1 (3.8)</td>
<td>14.2 (3.3)</td>
</tr>
<tr>
<td>Mean Change Week 12 (SD)</td>
<td>-6.46 (0.14)</td>
<td>-6.66 (0.28)</td>
<td>-9.40 (5.73)</td>
</tr>
<tr>
<td>Difference in LS means vs. placebo</td>
<td>-2.96</td>
<td>-2.95</td>
<td>-5.80</td>
</tr>
<tr>
<td>95% CI for difference</td>
<td>-4.71, -1.21</td>
<td>-4.72, -1.18</td>
<td>-7.49, -4.10</td>
</tr>
</tbody>
</table>

- Per the EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis, and management of urticaria the recommended starting dose of Omalizumab (Xolair) for CIU is 300 mg every 4 weeks.
- 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.

VI. 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.

VII. 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).

<table>
<thead>
<tr>
<th>POLYP 1</th>
<th></th>
<th>POLYP 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO N=66</td>
<td>OMA N=72</td>
<td>Treatment Difference (95% CI), p-value</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPS (range, 0-8)</td>
<td>0.06 (0.16)</td>
<td>-1.08 (0.16)</td>
<td>-1.14 (-1.59 to -0.69) p&lt;0.0001</td>
</tr>
<tr>
<td>NCS (range, 0-3)</td>
<td>-0.35 (0.11)</td>
<td>-0.89 (0.1)</td>
<td>-0.55 (-0.84 to -0.25) p&lt;0.0004</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNOT-22 score (range, 0-110)</td>
<td>-8.58 (2.08)</td>
<td>-24.70 (2.01)</td>
<td>-16.12 (-21.86 to -10.38) p&lt;0.0001</td>
</tr>
<tr>
<td>UPSIT score (range, 0-40)</td>
<td>0.63 (0.90)</td>
<td>4.44 (0.84)</td>
<td>3.81 (1.38-6.24) p&lt;0.0024</td>
</tr>
<tr>
<td>AQLQ score, OR of MCID (≥0.5-point improvement)</td>
<td>OR 3.71 (95% CI 1.13-13.71, p=0.0492)</td>
<td>OR 4.04 (95% CI 1.07-15.25, p=0.0396)</td>
<td></td>
</tr>
</tbody>
</table>

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.

VIII. Abbreviated list of H1 antihistamine products:

**H1 Antihistamine Products (not all inclusive)**

- fexofenadine
- loratadine
- desloratadine
- cetirizine
- levocetirizine
- clemastine
- diphenhydramine
- chlorpheniramine
- hydroxyzine
- cyproheptadine
- brompheniramine
- triprolidine
- dexchlorpheniramine
- carbinoxamine

Investigational or Not Medically Necessary Uses

1. 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. Ongoing clinical trials for the following conditions without outcomes demonstrating efficacy of treatment:
   i. Esophagitis
   ii. Interstitial cystitis
   iii. Painful bladder syndrome
   iv. Eosinophilic bronchitis
   v. Multi-food oral immunotherapy
   vi. Bullous pemphigoid
   vii. Peanut allergy
   viii. Chronic spontaneous urticaria
   ix. Solar urticaria
   x. Chronic urticaria
   xi. Cholinergic urticaria
   xii. Seasonal allergic rhinitis

Appendix

I. Table 1: Indication and dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Asthma</td>
<td>75 to 375 mg administered subcutaneously by a health care provider 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.</td>
</tr>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>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.</td>
</tr>
<tr>
<td>Chronic rhinosinusitis with nasal polyposis</td>
<td>75 to 600 mg SC administered subcutaneously by a health care provider 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.</td>
</tr>
<tr>
<td>All other indications</td>
<td>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.</td>
</tr>
</tbody>
</table>

II. Table 2: Weight based dosing every 4 weeks in members ≥ 12 years

<table>
<thead>
<tr>
<th>Omalizumab Doses Administered Every 4 Weeks (mg) in members ≥ 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington State Rx Services is administered by moda HEALTH</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>September 01, 2022</td>
</tr>
<tr>
<td>Pre-treatment serum IgE (IU/mL)</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>≥ 30 to 100</td>
</tr>
<tr>
<td>&gt; 100 to 200</td>
</tr>
<tr>
<td>&gt; 200 to 300</td>
</tr>
</tbody>
</table>

### III. Table 3: Weight based dosing every 2 weeks in members ≥ 12 years

<table>
<thead>
<tr>
<th>Pre-treatment serum IgE (IU/mL)</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 to 60</td>
</tr>
<tr>
<td>&gt; 100 to 200</td>
<td>See previous table.</td>
</tr>
<tr>
<td>&gt; 200 to 300</td>
<td>See previous table.</td>
</tr>
<tr>
<td>&gt; 300 to 400</td>
<td>225</td>
</tr>
<tr>
<td>&gt; 400 to 500</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 500 to 600</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 600 to 700</td>
<td>375</td>
</tr>
</tbody>
</table>

### IV. Table 4: Weight based dosing every 2 or 4 weeks for in members who begin Xolair between the ages of 6 to <12 years

<table>
<thead>
<tr>
<th>Pre-treatment IgE (IU/mL)</th>
<th>Dosing Freq. (weeks)</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-25</td>
<td>&gt;25-30</td>
</tr>
<tr>
<td>30-100</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>&gt;100-200</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>&gt;200-300</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>&gt;300-400</td>
<td>225</td>
<td>225</td>
</tr>
</tbody>
</table>
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.
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 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.

Previous reviews

Policy created
01/2012
Policy Type: PA  
Pharmacy Coverage Policy: UMP180

Description
The Omnipod Insulin Systems (Omnipod 5 [G6], Omnipod Dash, Omnipod Classic) are insulin delivery systems used to manage blood glucose in patients with diabetes mellitus that are insulin dependent.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipod Intro Kit</td>
<td>Diabetes Mellitus</td>
<td>Kit</td>
<td>1 kit/year</td>
</tr>
<tr>
<td>Omnipod Pod Refill</td>
<td>Diabetes Mellitus</td>
<td>Pods</td>
<td>15 pods/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. **Omnipod Insulin Systems (Omnipod 5 [G6], Omnipod Dash, Omnipod Classic)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of one of the following:
      1. **Type I Diabetes Mellitus**; OR
      2. **Type II Diabetes Mellitus**; AND
         i. Member is insulin dependent; AND
         ii. Documentation of multiple injections of insulin per day (e.g. more than 2 injections per day); AND
         iii. Documentation of member ability to self-test glucose at least 4 times daily while on insulin; AND
         iv. Documentation of member inability to self-inject insulin (e.g. unable to draw insulin from a vial or handle insulin pen); OR
            a. Documentation of member inability to self-adjust insulin dose (e.g. sliding scale dosing).

II. **Omnipod Insulin Systems (Omnipod 5 [G6], Omnipod Dash, Omnipod Classic)** is considered not medically necessary when criteria above are not met and/or when used for:
   A. Non-insulin dependent Type II Diabetes Mellitus
Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., management of blood glucose levels, A1c].

Supporting Evidence

I. Omnipod is an insulin delivery system that can provide up to 72 hours of continuous insulin delivery. It is a wearable Pod that is waterproof and can be worn anywhere the member would administer an injection. The Omnipod Dash system is designed to use rapid-acting U-100 insulin which the member would fill into the Pod. The Pod receives insulin delivery instructions from the Personal Diabetes Manager (PDM), a handheld device that controls and monitors the Pod’s operations using wireless technology.

II. The pods are sold in a box of 5, and per the Omnipod user handbook, it is recommended to change the pod every 48-72 hours.

Investigational or Not Medically Necessary Uses

I. Non-insulin dependent Type II Diabetes Mellitus

   A. Use of Omnipod Insulin Systems (Omnipod 5 [G6], Omnipod Dash, Omnipod Classic) are not medically necessary for Type II Diabetes Mellitus in members that are not dependent on insulin.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated policy to accommodate new generations of the Omnipod insulin system</td>
<td>05/2022</td>
</tr>
<tr>
<td>Policy updated to add Omnipod and increase quantity level limits to allow every 48-hour change</td>
<td>03/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>04/2020</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylnaltrexone bromide (Relistor)</td>
<td>150 mg tablets</td>
<td>Treatment of opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>90 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>12 mg vial/syringe</td>
<td>Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation</td>
<td>30 single use vials or syringes/30 days</td>
</tr>
<tr>
<td></td>
<td>8 mg vial/syringe</td>
<td></td>
<td>30 single use vials or syringes/30 days</td>
</tr>
<tr>
<td>naldemedine (Symproic)</td>
<td>0.2 mg tablets</td>
<td>Treatment of opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>naloxegol (Movantik)</td>
<td>12.5 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>25 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>

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
b. naldemedine (Symproic)

II. Methylaltrexone (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. Methylaltrexone 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. Methylaltrexone 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. Methylaltrexone 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). Methylaltrexone bromide (Relistor) injection demonstrated a statistically
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
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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated criteria for Movantik and Symproic from requiring trial and failure of two OTC alternatives to one</td>
<td>01/2022</td>
</tr>
<tr>
<td>Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents</td>
<td>11/2019</td>
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<tr>
<td>Previous Reviews</td>
<td>01/2018; 02/2018; 03/2018</td>
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</table>

Washington State Rx Services is administered by moda HEALTH

*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.*
Oral Iron Chelating Agents

**Policy Type: PA/SP**

**Pharmacy Coverage Policy: UMP017**

**Description**

Deferasirox (Exjade, Jadenu), and deferasiprone (Ferriprox) are orally administered iron chelating agents.

**Length of Authorization**

- Initial: Three months
- Renewal: 12 months

**Quantity limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deferasirox</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(generic Exjade)</td>
<td>125 mg tablet for suspension</td>
<td>Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome</td>
<td>Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 20 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>250 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deferasirox</strong></td>
<td>125 mg tablet for suspension</td>
<td>Hemosiderosis (chronic iron overload) – transfusion thalassemia</td>
<td>Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day</td>
</tr>
<tr>
<td>(Exjade)</td>
<td>250 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deferasirox</strong></td>
<td>90 mg tablet</td>
<td>Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome</td>
<td>Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 14 mg/kg per day</td>
</tr>
<tr>
<td>(generic Jadenu)</td>
<td>180 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90 mg granule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>180 mg granule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg granule</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deferasirox</strong></td>
<td>90 mg tablet</td>
<td>Hemosiderosis (chronic iron overload) – transfusion thalassemia</td>
<td>Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day</td>
</tr>
<tr>
<td>(Jadenu)</td>
<td>180 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90 mg granule (sprinkle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>180 mg granule (sprinkle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg granule (sprinkle)</td>
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<tr>
<td></td>
<td>500 mg tablet</td>
<td>Hemosiderosis</td>
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</tbody>
</table>
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**

---

<table>
<thead>
<tr>
<th>deferiprone (generic Ferriprox)</th>
<th>1000 mg tablet</th>
<th>(chronic iron overload) – transfusion thalassemia and transfusions related to sickle cell disease or other anemias</th>
<th>Monthly quantity to allow for a maximum of 99 mg/kg per day</th>
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<tr>
<td>deferiprone (Ferriprox)</td>
<td>100 mg/1 mL solution</td>
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<td></td>
<td>80 mg/1 mL solution</td>
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<td></td>
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<td></td>
<td>500 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 mg tablet</td>
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</tr>
</tbody>
</table>

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.

September 01, 2022
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**
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 an 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added 1000mg strength of deferiprone (generic Ferriprox)</td>
<td>02/2022</td>
</tr>
<tr>
<td>Addition of generic deferasirox oral granules and generic deferiprone tablets to policy;</td>
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<tr>
<td>requirement to have trial and failure or contraindication to both generic Exjade and Jadenu</td>
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</tr>
<tr>
<td>for prior to payment consideration of generic deferiprone, and generic Exjade and Jadenu</td>
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</tr>
<tr>
<td>AND generic deferiprone prior to payment consideration for brand Ferriprox. Criteria</td>
<td>09/2021</td>
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<tr>
<td>updated regarding the following: age for use of deferiprone tablets (8 years old) and</td>
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<td>deferiprone solution (3 years old), addition of LIC as baseline and renewal</td>
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<tr>
<td>measurement for transfusional iron overload. Update to supporting evidence.</td>
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<tr>
<td>Addition of generic Jadenu and new strength of deferiprone to the policy, with</td>
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<td>requirement to have trial and failure or contraindication, to both generic Exjade and</td>
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<td>documentation, ferritin level documentation, addition of a policy to Jadenu, specialist</td>
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<td>prescribing, additional of generic deferasirox (Exjade) tablet for oral suspension and</td>
<td></td>
</tr>
<tr>
<td>step through this product. Transition to policy format.</td>
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<td>Criteria created</td>
<td>08/2013</td>
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</table>
Osilodrostat (Isturisa®) is an orally administered cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>osilodrostat</td>
<td>1 mg tablets</td>
<td>Cushing’s disease</td>
<td>180 tablets/30 days</td>
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<td>5 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Osilodrostat (Isturisa) 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 endocrinologist; AND
   C. Documentation of baseline Urinary Free Cortisol (UFC) level; AND
   D. A diagnosis of Cushing’s disease when the following are met:
      1. Pituitary surgery is not an option OR cortisol levels remain abnormal following attempted resection; AND
      2. Treatment with TWO of the following has been ineffective, not tolerated, or all are contraindicated:
         i. Ketoconazole; OR
         ii. Cabergoline (Dostinex); OR
         iii. Metyrapone (Metopirone); OR
         iv. Mitotane (Lysodren); AND
      3. Treatment with pasireotide (Signifor) has been ineffective, contraindicated, or not tolerated.

II. Osilodrostat (Isturisa) 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 (e.g., cortisol level has decreased from baseline)

Supporting Evidence

I. The safety and efficacy of osilodrostat (Isturisa) has been studied inpatients 18 years of age or older, and there is no published data to support its use in pediatric patients.

II. Cushing’s disease is a serious and complex disease state that requires the supervision of a specialist (e.g. endocrinologist).

III. Cushing’s disease is a condition of pathological hypercortisolism that includes demonstrable clinical features. The goals of treating are to eliminate its primary cause and achieve remission so as to eliminate the associated signs, symptoms, and comorbidities and to improve quality of life (QOL).

IV. Osilodrostat (Isturisa) is indicated for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.

V. Osilodrostat (Isturisa) was studied in one prospective, multicenter, open-label, phase III trial with a double-blind, placebo-controlled, randomized withdrawal period in 137 patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.
   o The primary efficacy outcome was the proportion of patients maintaining complete response a mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) without a dose increase during the randomized withdrawal period at week 34.
   o At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC ≤ ULN). At the end of the 8-week randomized withdrawal period (Week 34 of study), the complete response rate in the osilodrostat (Isturisa) group dropped to 86.1% but was higher than that in the placebo group (29.4%).
   o The key secondary endpoint was the proportion of patients with mUFCsULN at week 24 (end of open-label osilodrostat treatment period 2) without dose-up titration weeks 13-24 and 72/137 patients met the endpoint

VI. According to the Endocrine Society Clinical Practice Guideline, first line treatment is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Medical therapy options within guidelines consist of steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed (i.e. cabergoline, pasireotide), and glucocorticoid antagonists (i.e. mifepristone). Guidelines do not prefer one medical therapy over another; however, guidelines do recommend glucocorticoid antagonists...
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.

VII. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other, however more established therapies include steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed (i.e. cabergoline, pasireotide) and glucocorticoid antagonists (i.e. mifepristone). The safety and efficacy of osilodrostat (Isturisa) was assessed in a 48-week long study. Long term safety and efficacy has not been established.

Investigational or Not Medically Necessary Uses

1. Osilodrostat (Isturisa) has not been FDA-approved, or sufficiently studied for safety and efficacy for any other conditions or settings except for patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.

References

1. Isturisa [Prescribing Information]. Recordati Rare Disease, Inc: Lebanon, NJ USA 08833. March 2020.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>07/2020</td>
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ospemifene (Osphena®)
UMP POLICY

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

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<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tbody>
<tr>
<td>ospemifene (Osphena)</td>
<td>60 mg tablets</td>
<td>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</td>
<td>30 tablets/30 days</td>
<td>178807</td>
</tr>
</tbody>
</table>

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. 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. Member has experienced symptomatic improvement (e.g., improvement in pain, discomfort, dryness, etc.)

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

Supporting Evidence

I. American College of Obstetricians and Gynecologists (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.

II. Ospemifene (Osphena) is classified as an impotence drug according to First Databank. This is considered a categorical exclusion in the prescription benefit structure; however, coverage is allowed in the setting of moderate to severe vaginal dryness outside of the dyspareunia setting.

III. 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

2. Diagnostic and Statistical Manual of Mental Disorders (DSM) Versions IV-TR and V.
3. Osphena [prescribing information]. Shionogi Inc.: Florham Park, NJ; March 2018

Policy Implementation/Update:

<table>
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<th>Date Created</th>
<th>February 2016</th>
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</tr>
<tr>
<td>Last Updated</td>
<td>September 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>03/2019, 09/2019</td>
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<table>
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<th>Action and Summary of Changes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Updated policy to remove coverage in the setting of dyspareunia as this is an excluded benefit.</td>
<td>09/2019</td>
</tr>
<tr>
<td>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.</td>
<td>03/2019</td>
</tr>
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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

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<tr>
<th>Product Name</th>
<th>Indication</th>
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<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>oteseconazole (Vivjoa)</td>
<td>Recurrent vulvovaginal candidiasis (RVVC) in females of non-reproductive potential</td>
<td>150mg capsules</td>
<td>18 capsules/84 days</td>
</tr>
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</table>

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. Treatment with weekly oral fluconazole for a period of 6 months is required; OR
         i. Treatment with fluconazole is not tolerated or contraindicated; OR
         ii. 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. Otoseconazole (Vivjoa) is an oral azole antifungal that has been FDA-approved to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC). Otoseconazole (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 otoseconazole (Vivjoa) or placebo for the maintenance period. The dosing of otoseconazole (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 otoseconazole (Vivjoa) or fluconazole/placebo. In the otoseconazole (Vivjoa) group, participants received 600mg on day one and 450mg on day two for induction therapy, then otoseconazole (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:

<table>
<thead>
<tr>
<th></th>
<th>Trial 1 (VIOLET)</th>
<th>Trial 2 (VIOLET)</th>
<th>Trial 3 (ultraVIOLET)</th>
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<tbody>
<tr>
<td>Induction regimen</td>
<td>OTE N = 217</td>
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<td>PBO N = 109</td>
<td>PBO N = 108</td>
<td>FLU/PBO N = 108</td>
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<td>Maintenance regimen</td>
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<td>OTE 150mg QD x7 days, then QW x11 weeks</td>
<td>OTE 150mg QD x7 days, then QW x11 weeks</td>
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<tr>
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<td>PBO</td>
<td>PBO</td>
<td>PBO</td>
</tr>
<tr>
<td>Proportion of patients with ≥1 culture-verified acute VVC episode (Day 1 – week 48)*</td>
<td>6.7%</td>
<td>42.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Proportion of patients with ≥1 culture-verified acute VVC episode</td>
<td>27.3%</td>
<td>50.8%</td>
<td>21.3%</td>
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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.

<table>
<thead>
<tr>
<th>acute VVC episode or received VVC medication (Day 1 – week 48)*</th>
<th>FLU = fluconazole 150mg on days 1, 4, and 7; PBO = matching placebo; OTE = oteseconazole</th>
</tr>
</thead>
</table>

*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, excoriations, 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 10-14-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, 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


Policy Implementation/Update:

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<td>08/2022</td>
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oxymetazoline (Upneeq™)
UMP POLICY

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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
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<tbody>
<tr>
<td>oxymetazoline (Upneeq)</td>
<td>0.1% solution</td>
<td>aponeurotic acquired blepharoptosis</td>
<td>30 dropperettes/30 days</td>
</tr>
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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 untapped; **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**
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 to 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.

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>RVL-1201-201 (n=140)</th>
<th>RVL-1201-202 (n=164)</th>
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<tr>
<td></td>
<td>Upneeq</td>
<td>Vehicle</td>
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<tr>
<td>Mean change in LPFT Day 1 (6 hours post instillation)</td>
<td>5.2 points</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Mean change in LPFT Day 14 (2 hours post instillation)</td>
<td>6.4 points</td>
<td>2.2 points</td>
</tr>
<tr>
<td>Mean change in MRD-1 from baseline (highest change; day 14, 2 hours post-instillation)</td>
<td>MRD-1 endpoints not published</td>
<td>1.3 mm</td>
</tr>
</tbody>
</table>

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


Policy Implementation/Update:

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<thead>
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<th>Action and Summary of Changes</th>
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<tbody>
<tr>
<td>Policy created</td>
<td>11/2020</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
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<th>Quantity Limit</th>
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<tbody>
<tr>
<td>pacritinib (Vonjo)</td>
<td>Intermediate- or high-risk myelofibrosis with severe thrombocytopenia (platelet count below 50 x 10⁹/L)</td>
<td>100 mg capsules</td>
<td>120 capsules/30 days</td>
</tr>
</tbody>
</table>

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 x 10⁹/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 ≥ 50 x 10⁹/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, symptomatic 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 ≥ 50 x 10^9/L. These medications are known to cause thrombocytopenia and are recommended to be discontinued if the platelet count drops below 50 x 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 x 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 x 10^9/L (45% had < 50 x 10^9/L). Regimens of 400 mg once daily and 200 mg twice daily were evaluated. Outcomes included spleen volume reduction (SVR) of ≥ 35%, and daily symptom score reduction of at least 50% via the MPN-SAF TSS tool. The trial indicated a
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.

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 x 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 x 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 x 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


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.
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.

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<td>ruxolitinib (Jakafi, Opzelura) Policy</td>
<td>Intermediate or high-risk myelofibrosis</td>
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<tr>
<td>fedratinib (Inrebic) Policy</td>
<td>Myelofibrosis</td>
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**Policy Implementation/Update:**

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<td>05/2022</td>
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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

<table>
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<th>Dosage Form</th>
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<tr>
<td>palivizumab (Synagis)</td>
<td>100 mg/1mL</td>
<td>Respiratory syncytial virus (RSV) prophylaxis</td>
<td>15 mg/kg (1 dose) per 28 days</td>
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<td>50 mg/0.5mL</td>
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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
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.

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 investigative 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 palicizumab (Synagis) for the treatment of RSV.

References

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: [link]
3. American Academy of Pediatrics: RSV recommendations unchanged after review of new data. Available at: [link]

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.

September 01, 2022


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>12/2020</td>
</tr>
<tr>
<td>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.</td>
<td>09/2019</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>panobinostat</td>
<td>10 mg capsules</td>
<td>Multiple Myeloma with ≥2 prior regimens, including bortezomib and an immunomodulatory agent</td>
<td>6 capsules/21 days</td>
</tr>
<tr>
<td>(Farydak)</td>
<td>15 mg capsules</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Prior use of immunomodulatory drugs (n=485)</th>
<th>PAN-BTZ-Dex</th>
<th>Placebo-BTZ-Dex</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Progression-Free Survival (95% CI, mo [n])</td>
<td>13.14 (11.56-15.47)</td>
<td>10.41 (7.95-11.53)</td>
<td>0.54 (0.43-0.68)</td>
</tr>
<tr>
<td>Prior use of immunomodulatory drugs and bortezomib (n=193)</td>
<td>11.99 (9.69-13.90)</td>
<td>8.31 (6.14-12.32)</td>
<td>0.52 (0.36-0.76)</td>
</tr>
<tr>
<td>Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)</td>
<td>11.99 (9.69-13.37)</td>
<td>6.97 (4.86-13.40)</td>
<td>0.47 (0.31-0.72)</td>
</tr>
</tbody>
</table>

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September 01, 2022
- 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.

<table>
<thead>
<tr>
<th>Prior use of immunomodulatory drugs (n=485)</th>
<th>Median Overall Survival (95% CI, mo [n])</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-BTZ-Dex</td>
<td>36.2 (31.18–41.36)</td>
<td>0.94 (0.74–1.19)</td>
</tr>
<tr>
<td>Placebo-BTZ-Dex</td>
<td>29.4 (24.57–37.78)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior use of immunomodulatory drugs and bortezomib (n=193)</th>
<th>Median Overall Survival (95% CI, mo [n])</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-BTZ-Dex</td>
<td>27.2 (24.21–34.63)</td>
<td>1.03 (0.72–1.47)</td>
</tr>
<tr>
<td>Placebo-BTZ-Dex</td>
<td>24.7 (17.48–35.38)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)</th>
<th>Median Overall Survival (95% CI, mo [n])</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-BTZ-Dex</td>
<td>25.5 (19.58–34.33)</td>
<td>1.01 (0.68–1.50)</td>
</tr>
<tr>
<td>Placebo-BTZ-Dex</td>
<td>25.5 (19.58–34.33)</td>
<td></td>
</tr>
</tbody>
</table>

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 than in the overall trial 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 (≥20%) are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting.
- Common non-hematologic abnormalities (≥40%) are hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine.
- Common hematologic abnormalities (≥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

<table>
<thead>
<tr>
<th>Cycles 1 to 8 (3-Week cycles)</th>
<th>Week 1 Days</th>
<th>Week 2 Days</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FARYDAK</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

II. Table 2: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 9 to 16

<table>
<thead>
<tr>
<th>Cycles 9 to 16 (3-Week cycles)</th>
<th>Week 1 Days</th>
<th>Week 2 Days</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FARYDAK</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1</td>
<td>8</td>
<td>Rest period</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

III. Table 3: Classification of Medications used for Multiple Myeloma

<table>
<thead>
<tr>
<th>Proteasome Inhibitors</th>
<th>Immunomodulatory Agents</th>
<th>Monoclonal Antibodies</th>
<th>Histone Deacetylase Inhibitors</th>
<th>B-cell Maturation Antigen-Directed Antibody</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>bortezomib</td>
<td>thalidomide</td>
<td>elotuzumab</td>
<td>belantamab mafodotin-blmf</td>
<td>cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>carfilzomib</td>
<td>lenalidomide</td>
<td>daratumumab</td>
<td>doxorubicin</td>
<td>doxorubicin</td>
<td></td>
</tr>
<tr>
<td>ixazomib</td>
<td>pomalidomide</td>
<td>isatuximab-irfc</td>
<td>cisplatin</td>
<td>cisplatin</td>
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<tr>
<td>panobinostat</td>
<td></td>
<td></td>
<td></td>
<td>etoposide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>melphalan</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bendamustine</td>
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</tr>
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References


Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)].</td>
<td>10/2020</td>
</tr>
<tr>
<td>Criteria created</td>
<td>03/2015</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone (Natpara)</td>
<td>25 mcg/dose cartridge</td>
<td>Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism</td>
<td>2 cartridges/28 days</td>
</tr>
<tr>
<td></td>
<td>50 mcg/dose cartridge</td>
<td></td>
<td>2 cartridges/28 days</td>
</tr>
<tr>
<td></td>
<td>75 mcg/dose cartridge</td>
<td></td>
<td>2 cartridges/28 days</td>
</tr>
<tr>
<td></td>
<td>100 mcg/dose cartridge</td>
<td></td>
<td>2 cartridges/28 days</td>
</tr>
</tbody>
</table>

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

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September 01, 2022
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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria updated to new policy format.</td>
<td>11/2019</td>
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</tbody>
</table>

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.
Policy Type: PA/SP

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>teriparatide (Forteo)</td>
<td>250 mcg/mL</td>
<td>Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men</td>
<td>1 syringe/28 days</td>
</tr>
<tr>
<td>teriparatide (biosimilar formulation)</td>
<td>250 mcg/mL</td>
<td>Post-Menopausal Osteoporosis in Women</td>
<td>1 syringe/28 days</td>
</tr>
<tr>
<td>abaloparatide (Tymlos)</td>
<td>2000 mcg/mL</td>
<td>Post-Menopausal Osteoporosis in Women</td>
<td>1 syringe/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Abaloparatide (Tymlos), teriparatide (biosimilar formulation), 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 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 probably for major fracture >30% or hip fracture >4.5%, etc.); AND
   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 T-score ≤ -2.5 in spine, femoral neck, total hip or 1/3 radius; OR

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.
2. Member has a T-score ≤ -1 and a history of recent fragility fracture to the hip or spine; OR
3. Member has a T-score between -1 and -2.5 with a FRAX 10-year probability for major fracture ≥20% or hip fracture ≥3%; AND
E. Documentation of treatment failure or ineffective response to a minimum 12-month trial of 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 teriparatide (biosimilar formulation) or teriparatide (Forteo), a diagnosis of one of the following:
   1. Post-Menopausal Osteoporosis in Women; AND
      i. If request is for teriparatide (biosimilar formulation), treatment with abaloparatide (Tymlos) has been ineffective, not tolerated or contraindicated; OR
      ii. If request is for teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; AND
         a. Treatment with abaloparatide (Tymlos) has been ineffective, not tolerated or contraindicated; OR
   2. Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND
      i. Request is for teriparatide (Forteo) and treatment with teriparatide (biosimilar formulation) has 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. If request is for teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; OR
G. For abaloparatide (Tymlos):
   1. A diagnosis of post-menopausal osteoporosis in women
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 primary osteoporosis/hypogonadal-related osteoporosis; OR 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. Member has not received treatment with parathyroid hormone for more than a total of two years during their lifetime; AND
   • 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

V. Member will have received treatment with a parathyroid hormone for more than two years during their lifetime; AND
   1. Provider attestation that patient remains or has returned to having 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 probably for major fracture >30% or hip fracture >4.5%, etc.)

Supporting Evidence

I. 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. 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 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 probably for major fracture >30% or hip fracture >4.5%, etc.

II. Osteoporosis in postmenopausal 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 recommend pharmacologic therapy for postmenopausal women with low bone mass and a history of hip or spine fragility fracture, a T-score of -2.5 or lower in spine, femoral neck, total hip or 1/3 radius or a T-score of -2.5 to -1.0 and a high FRAX risk score (major osteoporosis fracture risk ≥20%, hip fracture risk ≥3%). Additionally, the treatment guidelines define very high fracture risk as a history of fracture within past 12 months, fracture while on osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (less than -3.0), high risk for falls or history of injurious falls, and/or very high fracture probability by FRAX (major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm; all other patients are considered high fracture risk. Treatment recommendations are as follows:

   a. Initial treatment for high fracture risk: alendronate, denosumab, risedronate, or zoledronate (strong recommendation, high quality evidence)

   b. 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).

   c. 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 antiresportive 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 Prolia are considered standard and appropriate high-value treatment options in this setting.

III. Primary or hypogonadal 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. 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. 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).

IV. 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; there is currently a lack of sufficient evidence regarding safety and efficacy in other settings.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>12/2021</td>
</tr>
<tr>
<td>Added criteria for the biosimilar teriparatide, requiring trial of the biosimilar prior to brand Forteo</td>
<td>11/2020</td>
</tr>
<tr>
<td>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</td>
<td>04/2020</td>
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<tr>
<td>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</td>
<td>02/2020</td>
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<tr>
<td>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</td>
<td>12/2019</td>
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and with fragility fracture, defined high risk fractures, and provided inclusion criteria for glucocorticoid-induced osteoporosis.

<table>
<thead>
<tr>
<th>Update criteria to include abaloparatide (Tymlos)</th>
<th>08/2017</th>
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</thead>
<tbody>
<tr>
<td>Date effective</td>
<td>03/2016</td>
</tr>
<tr>
<td>Policy created</td>
<td>09/2005</td>
</tr>
</tbody>
</table>
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.

Pasireotide diaspartate (Signifor®) is a subcutaneous somatostatin analog solution that exerts its activity by binding to somatostatin receptors causing adrenocorticotropic hormone (ACTH) secretion to be inhibited thereby leading to decreased cortisol secretion.

**Length of Authorization**
- **Initial**: Six months
- **Renewal**: 12 months

**Quantity Limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pasireotide</td>
<td>0.3 mg/mL ampule</td>
<td>Cushing’s disease</td>
<td>60 ampules/30 days</td>
</tr>
<tr>
<td>diaspartate</td>
<td>0.6 mg/mL ampule</td>
<td></td>
<td>60 ampules/30 days</td>
</tr>
<tr>
<td>(Signifor)</td>
<td>0.9 mg/mL ampule</td>
<td></td>
<td>60 ampules/30 days</td>
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<tr>
<td>pasireotide</td>
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<td>Acromegaly</td>
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<tr>
<td>pamoate</td>
<td>40 mg vial</td>
<td>Cushing’s disease</td>
<td></td>
</tr>
<tr>
<td>(Signifor LAR)</td>
<td>60 mg vial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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. Pasireotide diaspartate (Signifor) 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 **Cushing’s disease** when the following are met:
      1. Pituitary surgery is not an option **OR** cortisol levels remain abnormal following attempted resection; **AND**
      2. Treatment with **TWO** of the following has been ineffective, not tolerated, or all are contraindicated:
         i. Ketoconazole; **OR**
         ii. Cabergoline (Dostinex); **OR**
         iii. Metyrapone (Metopirone); **OR**
         iv. Mitotane (Lysodren)

II. Pasireotide diaspartate (Signifor) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Acromegaly

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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.

September 01, 2022
B. Pancreatic fistula, postoperative/prophylaxis
C. Carcinoid syndrome
D. Neuroendocrine tumor

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline)

Supporting Evidence

I. Cushing’s disease is a disorder that leads to excess cortisol and is usually due to a corticotropin (ACTH)-producing pituitary tumor. Goals of treatment include the reversal of clinical manifestations by normalizing cortisol secretion, damaging tumor eradication, and avoidance of permanent hormone deficiency which can leave a permanent dependence upon medications. The excess cortisol of Cushing’s disease is primarily treated with transsphenoidal surgery (TSS) regardless of its cause. Although surgical treatment is optimal, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Adrenal enzyme inhibitors are the most commonly used medications; however, adrenolytic agents, drugs that target a pituitary or ectopic tumor, and glucocorticoid-receptor antagonists have also been used.

II. Pasireotide diaspartate (Signifor) is indicated for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.

III. Endocrine Society guidelines recommend medical therapy in cases were surgery is delayed, contraindicated, or unsuccessful. Medical therapy options within guidelines consist of steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed treatments (i.e. cabergoline, pasireotide), and glucocorticoid antagonists (i.e. mifepristone). Guidelines do not prefer one medical therapy over another; however, guidelines do recommend glucocorticoid antagonists (i.e. mifepristone) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS.

Investigational or Not Medically Necessary Uses

I. Acromegaly
   A. Pasireotide diaspartate (Signifor) does not carry an FDA approval in the setting of acromegaly; however, the pasireotide pamoate (Signifor LAR) product is available in this setting.
   B. Pancreatic fistula, postoperative; prophylaxis
      i. Limited data shows reduction in relative risk only.
   C. Carcinoid syndrome
      i. Agent fails to improve symptom control or tumor response.
D. Neuroendocrine tumor
   i. Agent fails to improve symptom control or tumor response; use is not recognized by NCCN guidelines.

References

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated the example for improvement or stability of disease symptoms</td>
<td>08/2020</td>
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<tr>
<td>Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.</td>
<td>12/2019</td>
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<tr>
<td>Criteria created</td>
<td>07/2013</td>
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</table>
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 peanut. The mechanism of action is unknown at this time.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>peanut allergen powder-dnfp (Palforzia)</td>
<td>0.5 mg – 6 mg capsule sprinkle</td>
<td>Peanut allergy</td>
<td>13 capsule sprinkles/1 day</td>
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<td>3 mg daily dose capsule sprinkle</td>
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<td></td>
<td>300 mg maintenance capsule sprinkle powder pack</td>
<td>Peanut allergy</td>
<td>30 capsule sprinkles/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Peanut allergen powder-dnfp (Palforzia) may be considered medically necessary when the following criteria are met:
   A. Member is four to 17 years of age and request is for initial dose escalation; OR
   1. Member is four 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 be 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 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

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 four to 17 years of age; **OR**
   A. Member is four years of age or older and is up-dosing or in maintenance; **AND**

IV. Must have current prescription for epinephrine; **AND**

V. Medication 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; **AND**

VIII. The medication will not 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. In the PALISADE 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 (~ 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.
III. 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”.

IV. The peanut allergen powder-dnfp (Palforzia) package insert and Risk Evaluation and Mitigation Strategy (REMS) program require peanut allergen powder-dnfp (Palforzia) 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.

V. 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, and abdominal pain in children; and dysphagia and esophageal food impactions in adolescents and adults. Eosinophilic esophagitis is a known complication of oral immunotherapy.

VI. 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.

VII. 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.

VIII. 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 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 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.

References


Policy Implementation/Update:

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<td>05/2020</td>
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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.
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP235

Description
Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>pegcetacoplan</td>
<td>1,080 mg/20 mL vial</td>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td>160 mL (8 vials)/28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Pegcetacoplan (Empaveli) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or immunologist; **AND**
   C. Provider attestation that therapy will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]) (Note: overlapping therapy to comply with switch therapy guidance is allowed, see Appendix); **AND**
   D. Provider attestation of a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed via flow cytometry; **AND**
   E. Member has at least one of the following indications for treatment (chart notes required):
      1. Transfusion dependence (hemoglobin is 7 g/dL or less)
      2. Hemoglobin is 9 g/dL or less with symptoms of anemia
      3. The member has experienced a thromboembolic event
      4. Presence of organ damage secondary to chronic hemolysis
      5. High LDH activity (≥ 1.5 x ULN) with clinical symptoms; **AND**
   F. Documentation of baseline value for ALL of the following (chart notes required, necessary for renewal):
      1. Hemoglobin
      2. LDH level
      3. Reticulocytes
      4. Number of transfusions over the last year

II. Pegcetacoplan (Empaveli) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients

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.
B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
C. Amyotrophic lateral sclerosis (ALS)
D. Glomerulopathy or glomerulonephritis
E. Macular degeneration
F. Hemolytic uremic syndrome
G. Myasthenia gravis
H. Neuromyelitis optica spectrum disorder (NMOSD)

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 medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]); **AND**

IV. Member has exhibited improvement or stability of disease symptoms as evidenced by at least one of the following:
   - Increase in hemoglobin
   - Reduction in LDH
   - Reduction in reticulocyte count
   - Reduction in transfusion frequency

Supporting Evidence

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

II. Diagnosis and treatment of this condition is highly specialized. To ensure appropriate diagnosis and that benefits of treatment outweigh risks, prescribing by, or in consultation with, a specialist is required. Confirmation of diagnosis by Flow Cytometry is currently the most accepted method to confirm diagnosis of PHN; this is required given the rarity of PNH and to ensure medication is medically necessary.

III. Treatment for PNH is indicated when signs and symptoms are present. This includes transfusion dependence, symptoms of anemia, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range.

IV. The C5 inhibitors, eculizumab (Soliris) and ravulizumab (Ultomiris) (± supportive care), have become standard of care given their ability to improve disease manifestations. However, these only target intravascular hemolysis, leaving opportunity for extravascular hemolysis in the liver and spleen. Despite treatment, anemia and need for continued blood transfusions may persist in some patients. For the majority of patients C5 inhibitors are successful treatment options as...
they have shown to improve Hg, LDH levels, reticulocyte count, and/or reduce transfusion frequency. The safety profile of these therapies is well established.

V. Pegcetacoplan (Empaveli) is a C3 complement inhibitor, and acts proximally to the complement cascade, preventing intravascular and extravascular hemolysis. It is the first complement inhibitor that may be self-administered - via a subcutaneous infusion pump. However, therapy may also be administered by a healthcare provider. Therapy that is being administered by a healthcare professional should be billed through the member’s medical benefit.

VI. To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy in pediatric patients. Other therapies [e.g., ravulizumab (Ultomiris)] have been evaluated and are FDA-approved down to one month of age. Until sufficiently evaluated in pediatric patients, pegcetacoplan (Empaveli) should be reserved for the FDA-approved age group(s) given the availability of alternatives avenues of care [e.g., other FDA-approved medications, enrolment in clinical trials].

VII. The pivotal trial for this therapy was an open-label, randomized, Phase 3 study in comparison to eculizumab (Soliris) (PEGASUS trial). Patients were 18 years of age or older, had a hemoglobin of less than 10.5 mg/dL (mean 8.7 g/dL) while on stable doses of eculizumab (Soliris) for at least three months before enrollment, 75% received a blood transfusion in the last year (over 50% of patients received four or more).

VIII. Eighty patients were enrolled in the trial. Seventy-five percent had received a blood transfusion in the last year (over 50% of patients received four or more). Primary outcome: change in Hg from baseline at week 16. Secondary outcomes: proportion of transfusion-free patients, change in reticulocyte count, lactate dehydrogenase (LDH) level, and Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The normalization of hematologic variables was also evaluated. Endpoints were tested in a hierarchical manner, the primary outcome was tested for superiority, and the secondary outcomes were tested for non-inferiority (NI). The primary outcome met superiority, and transfusion rate and reticulocyte count met NI. Normalization of hematologic variables (Hg, reticulocytes, LDH) were favorable for pegcetacoplan (Empaveli). Pegcetacoplan (Empaveli) was also evaluated in Phase 1 and 2 open-label, single-arm trials in complement inhibitor-naive patients. Improvements were seen in Hg, LDH, reticulocytes, and FACIT-F scores in a small number of patients.

IX. The safety and efficacy of pegcetacoplan (Empaveli) has been established for 1,080 mg (20 mL) twice weekly. In the clinical trials, three patients discontinued therapy given lack of efficacy. Following, a protocol amendment was made to allow an increase in the dose to every three days, and two patients received the increased dose. Data regarding safety and efficacy of greater than 1,080 mg (20 mL) twice weekly has not been disclosed and real-world studies are underway to evaluate increasing the frequency to every three days.

X. With the exception of the four-week overlap to get patients established on pegcetacoplan (Empaveli), therapy has not been evaluated in combination with other complement inhibitors. It is advised that complement inhibitors are not abruptly discontinued. If switching from eculizumab (Soliris), therapy should be overlapped for four weeks with pegcetacoplan (Empaveli). For those switching from ravulizumab (Ultomiris), pegcetacoplan (Empaveli) should be started no more than four weeks after the last dose of ravulizumab (Ultomiris). Maintenance therapy with more than one complement inhibitor therapy is not expected to have additional efficacy, and is expected to have serious safety implications [e.g., serious infections caused by encapsulated bacteria]. Thus, maintenance on more than one complement inhibitor therapy is not indicated at this time.

XI. The bulk of evidence is from patients that were refractory to C5 inhibitor, eculizumab (Soliris), and it is expected that pegcetacoplan (Empaveli) will be utilized heavily in this treatment setting;
however, given the alternative protein target of this therapy, coupled with evidence data support from Phase 1 and 2 trials, it is expected pegcetacoplan (Empaveli) will be efficacious as a first-line treatment. A clinical trial is underway to evaluate this further.

**Investigational or Not Medically Necessary Uses**

I. Pegcetacoplan (Empaveli) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
   C. Amyotrophic lateral sclerosis (ALS)
   D. Glomerulopathy or glomerulonephritis
   E. Macular degeneration
   F. Hemolytic uremic syndrome
   G. Myasthenia gravis
   H. Neuromyelitis optica spectrum disorder

**Appendix**

I. Complement inhibitor administration:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose/Frequency</th>
<th>Duration of medication coverage (maintenance)</th>
<th>Route</th>
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<tbody>
<tr>
<td>pegcetacoplan (Empaveli)</td>
<td>1,080 mg (20 mL) twice weekly</td>
<td>3-4 days</td>
<td>SQ</td>
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<tr>
<td>eculizumab (Soliris)</td>
<td>600 mg weekly for four weeks, 900 mg on the fifth week, then 900 mg every two weeks thereafter</td>
<td>2 weeks</td>
<td>IV</td>
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<tr>
<td>ravulizumab (Ultomiris)</td>
<td>One loading dose (based on weight) 2,400 mg-3,000 mg, then maintenance treatment (based on weight) starting two weeks later: 3,000 mg – 3,600 mg every eight weeks</td>
<td>8 weeks</td>
<td>IV</td>
</tr>
</tbody>
</table>

II. Switch therapy guidance:

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

References


Policy Implementation/Update:

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<td>Policy created</td>
<td>08/2021</td>
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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

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<td>peginterferon alfa-2b (Sylatron)</td>
<td>200 mcg subcutaneous powder for solution</td>
<td>Adjuvant treatment of melanoma with microscopic or gross nodal involvement</td>
<td>4 vials/28 days</td>
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<td>300 mcg subcutaneous powder for solution</td>
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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.
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


Policy Implementation/Update:

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<tr>
<td>Date Effective</td>
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<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
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<td>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.</td>
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**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:**
  - For Polycythemia Vera AND Essential Thrombocythemia: 12 months
  - For all other indications: None

**Quantity limits**

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>Peginterferon Alfa-2a (Pegasys; Pegasys ProClick)</td>
<td>180 µg/mL vial</td>
<td>Chronic Hepatitis B; Chronic Hepatitis D; Polycythemia Vera; Essential Thrombocythemia</td>
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<td>180 µg/0.5 mL prefilled syringe</td>
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<td>180 µg/0.5 mL autoinjector</td>
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<td>4 autoinjectors/30 days</td>
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**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**
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 Peg-interferon, 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.
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-a). 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 10^9/L in ET and >1000 X 10^9/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 AALSD 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...
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.
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
7. U.S. National Library of Medicine; Clinical Trials database; NCT01259856; NCT00452023; NCT00241241; https://clinicaltrials.gov

Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>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</td>
<td>12/2020</td>
</tr>
<tr>
<td>Criteria created</td>
<td>01/2006</td>
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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.
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

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<th>Indication</th>
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<tr>
<td>pegvisomant (Somavert)</td>
<td>10 mg vial</td>
<td>Acromegaly</td>
<td>60 vials/30 days</td>
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<tr>
<td></td>
<td>15 mg vial</td>
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<td>60 vials/30 days</td>
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<td></td>
<td>20 mg vial</td>
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<tr>
<td></td>
<td>25 mg vial</td>
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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.

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.
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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>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.</td>
<td>05/2020</td>
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<tr>
<td>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.</td>
<td>12/2019</td>
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<td>01/2006</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP191

Description
Pemigatinib (Pemazyre™) is an orally administered fibroblast growth factor receptor 2 (FGFR2) inhibitor, with activity against FGFR2 fusions or rearrangements in cholangiocarcinoma cells.

Length of Authorization
- N/A

Quantity Limits

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<tr>
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<tr>
<td>Pemigatinib (Pemazyre)</td>
<td>13.5 mg tablet</td>
<td>Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements</td>
<td>14 tablets/21 days</td>
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<td>9 mg tablet</td>
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<td>4.5 mg tablet</td>
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Initial Evaluation

I. Pemigatinib (Pemazyre) is considered investigational when used for all conditions, including but not limited to cholangiocarcinoma.

Renewal Evaluation

I. N/A

Supporting Evidence

I. Pemigatinib (Pemazyre) is the first targeted therapy for cholangiocarcinoma that harbors FGFR2 fusions or rearrangements. Pemigatinib (Pemazyre) is a second-line chemotherapy option. Guideline preferred first line chemotherapy is gemcitabine and cisplatin, while second-line options include mFOLFOX, FOLFIRI, and regorafenib (Stivarga).

II. Pemigatinib (Pemazyre) was evaluated in FIGHT-202, an open-label, single-arm, multi-cohort Phase 2 trial. Patients (N=146) with locally advanced or metastatic CCA, previously treated with at least 1 chemotherapy were included. FDA approval was based on the overall response rate (ORR) in patients with FGFR2 gene fusion or rearrangements.

III. The primary efficacy endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of...
comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

IV. Pemigatinib (Pemazyre) received accelerated approval from the FDA based on ORR and DOR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 3 trial underway to assess pemigatinib (Pemazyre) monotherapy versus gemcitabine + cisplatin in the first-line treatment of CCA with FGFR2 alterations.

V. The safety profile of pemigatinib (Pemazyre) was based on adverse reactions observed in all cohorts during CT (N=146). The most common adverse events (≥20% incidence) included hyperphosphatemia, alopecia, nausea, diarrhea, nail toxicity, back pain, fatigue, dysgeusia, dry eyes, and serous retinal detachment. There are no specific contraindications to pemigatinib (Pemazyre); however, warnings and precautions include: ocular toxicity, hyperphosphatemia, GI toxicity and renal function. Pemigatinib (Pemazyre) showed 9% treatment discontinuation rate, 14% dose reductions rate, and 42% dose interruption rate due to adverse events.

VI. As of June 2020, The National Comprehensive Cancer Network (NCCN) treatment guideline for hepatobiliary cancer has included pemigatinib (Pemazyre) as second-line treatment with a Category 2A recommendation. Pemigatinib (Pemazyre) is useful in treatment of tumor with confirmed FGFR2 fusions or rearrangements; and which are refractory to first line chemotherapy.

Investigational or Not Medically Necessary Uses

I. Pemigatinib (Pemazyre) has not been sufficiently studied for safety and efficacy for any other condition to date.

References

10. Abou-alfa GK et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicenter, open-label, phase 2 study. Lancet Oncol. 2020 May;21(5):671-684. (NCT02924376)

Policy Implementation/Update:

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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.
Policy Type: PA/SP
Pharmacy Coverage Policy: UMP085

Split Fill Management*

Description
Pexidartinib (Turalio) is an oral kinase inhibitor FDA-approved for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Length of Authorization
- Initial: Six months, split fill for the first three months
- Renewal: 12 months

Quantity limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>pexidartinib (Turalio)</td>
<td>200 mg capsule</td>
<td>Tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery</td>
<td>120 capsules/30 days</td>
<td>207496 207495</td>
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Initial Evaluation

I. Pexidartinib (Turalio) 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. Member has a confirmed diagnosis of symptomatic tenosynovial giant cell tumor; **AND**
   D. A surgical/orthopedic oncologist or orthopedic surgeon has evaluated that the member is not a candidate for surgery; **AND**
   E. Member does **not** have preexisting increased serum transaminases such as ALT and AST or an indication of hepatotoxicity; **AND**
   F. The medication is used as a monotherapy
II. Pexidartinib (Turalio) is 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. Pexidartinib (Turalio) is 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**

I. Pexidartinib (Turalio) may be considered for continuation of therapy when the following criteria below are met:
   A. Member has an absence of unacceptable toxicity from the medication; **AND**
   B. Clinical documentation showing symptomatic/disease improvement(s) including
      1. Stable or improved range of motion of affected joint; **OR**
      2. Stable or improved pain in affected joint; **OR**
      3. Stable or improved in stiffness of affected joint

**Supporting Evidence**

I. Pexidartinib (Turalio) is FDA-approved for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

II. Tenosynovial giant cell tumor is also referred to as giant cell tumor of the tendon sheath (GCTTS) or pigmented villonodular synovitis (PVNS).

III. Patients with recurrent and/or relapsed TGCT may typically undergo surgical interventions, however, if further surgery would result in significant morbidity or functional impairment, systemic therapy such as pexidartinib (Turalio) may be beneficial.

IV. Pexidartinib (Turalio) was studied in a 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. Pexidartinib (Turalio) has boxed warnings and REMS program for the risk of serious and potentially fatal liver injury and embryo-fetal toxicity.

VI. 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%).

VII. 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.

VIII. In the clinical trial (ENLIVEN), pexidartinib (Turalio) was used as a single-agent therapy.

Investigational or Not Medically Necessary Uses

I. All condition(s) listed as investigational use
   A. These conditions are parts of the exclusion criteria from the ENLIVEN clinical trial. Safety and efficacy of pexidartinib (Turalio) for these conditions are not studied and unknown.

* 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


Policy Implementation/Update:

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<td>09/2019</td>
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Phenylketonuria Agents
UMP POLICY

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

<table>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>pegvaliase (Palynziq)</td>
<td>2.5 mg/0.5 mL</td>
<td>Phenylketonuria (PKU)</td>
<td>8 syringes/30 days</td>
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<td>10 mg/0.5 mL</td>
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<td>30 syringes/30 days</td>
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<tr>
<td></td>
<td>20 mg/1 mL</td>
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<td>90 syringes/30 days</td>
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<tr>
<td>sapropterin dihydrochloride (generic Kuvan)</td>
<td>100 mg tablets</td>
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<td>20 mg/kg/day</td>
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<td></td>
<td>100 mg powder for oral solution</td>
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Initial Evaluation

I. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) 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 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
      2. Request is for sapropterin dihydrochloride (Kuvan); **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. 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**

IV. Documentation noting member compliance with a phenylalanine restricted diet; **AND**

V. Documentation of current blood phenylalanine concentration is submitted; **AND**
VI. Attestation of member compliance to therapy with pegvaliase (Palynziq) or sapropterin dihydrochloride (Kuvan); **AND**

VII. Member had a response to pegvaliase (Palynziq) therapy defined as:
- At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
- Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**

VIII. Member had a response to sapropterin dihydrochloride (Kuvan) therapy defined as:
- At least a 30% reduction in blood phenylalanine levels from baseline

**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. 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.

III. 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. 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.

IV. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine prior to treatment start.

V. 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.

VI. Pegvaliase (Palynziq) is indicated 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)].

VII. 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 age 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 age 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 age <18 years, and possible safety concerns, thus true safety and efficacy of Palynziq in the subset of patients age 16 to 18 years remains unknown.

VIII. 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).

IX. Sapropterin dihydrochloride (Kuvan) is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU. Kuvan is to be used in conjunction with a Phe-restricted diet.

**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 need to support use of sapropterin dihydrochloride (Kuvan) in this setting.
References

   Accessed 01/19/2009.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>10/2021</td>
</tr>
</tbody>
</table>
- 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

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegvaliase (Palynziq) policy</td>
<td>08/2018</td>
</tr>
<tr>
<td>Sapropterin dihydrochloride (Kuvan) policy</td>
<td>02/2009</td>
</tr>
</tbody>
</table>

September 01, 2022
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP053

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

Length of Authorization
- Initial: six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>pimavanserin (Nuplazid)</td>
<td>34 mg capsules</td>
<td>Parkinson’s disease psychosis</td>
<td>30 capsules/30 days</td>
<td>203479, 203276</td>
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<tr>
<td></td>
<td>17 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
<td>192903, 192710</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
<td>203478, 203281</td>
</tr>
</tbody>
</table>

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

Renewal Evaluation
I. Noted reduction in delusions and hallucinations.
Supporting Evidence

I. Pimavanserin (Nuplazid) is indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis for patients 18 years of age and older.

II. Pimavanserin (Nuplazid) was studied in a 6-week, randomized, placebo-controlled, parallel-group study in 199 patients with a diagnosis of Parkinson’s disease (PD) and psychotic symptoms.
   - The primary efficacy outcome was the change from baseline to week 6 in a PD-adapted scale for the assessment of positive symptoms (SAPS-PD).
   - A positive effect was seen on both hallucination and delusion components of the SAPS-PD for pimavanserin (Nuplazid) versus placebo [-3.06 (-4.91, -1.2)]. Although statistically significant, the clinical relevance of this result is unclear.
   - No difference in motor function was observed between pimavanserin (Nuplazid) and placebo.

III. Pimavanserin (Nuplazid) was studied in multiple unpublished clinical trials that either failed to demonstrate efficacy or were terminated early due to trial failure.

IV. Pimavanserin (Nuplazid) was FDA-approved under the breakthrough therapy and priority review designation where preliminary clinical evidence indicated pimavanserin (Nuplazid) may demonstrate substantial improvement over current available therapies. In addition, the FDA-medical reviewer recommended against FDA-approval.

V. Clozapine has been studied in two four-week, placebo-controlled trials, as well as, two smaller trials comparing clozapine and quetiapine. Clozapine demonstrated improved global impression scores, improved psychotic symptom assessment scores, and similar motor and cognitive function compared with patients on placebo.

VI. The Movement Disorder Society rated clozapine as more efficacious compared to quetiapine which was deemed to have insufficient evidence, and does not make any recommendation on pimavanserin (Nuplazid).

References

**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Date Created</th>
<th>July 2016</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>August 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>September 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>September 2019</td>
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</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition from criteria to policy: Included requirements to attempt dose reduction in parkinson’s medications, and specified what members must try and fail.</td>
<td>September 2019</td>
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</table>
Policy Type: PA/SP                   Pharmacy Coverage Policy: UMP225

Split Fill Management*

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

Length of Authorization
- Initial: three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication*</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ponatinib (Iclusig)</td>
<td>10 mg tablet</td>
<td>CP-CML with resistance or intolerance to two prior kinase inhibitors; AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated; T315I-positive CML (any phase) or T315I-positive Ph+ ALL</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>15 mg tablet</td>
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</tr>
<tr>
<td></td>
<td>45 mg tablet</td>
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<td>30 tablets/30 days</td>
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</tbody>
</table>

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

Initial Evaluation

I. Ponatinib (Iclusig) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; AND
   C. Medication is not used in combination with any other oncology therapy; AND
   D. A diagnosis of **Chronic Phase-Chronic Myeloid Leukemia (CP-CML); AND**
      1. Documented resistance, or intolerance to, two prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif)); OR
      2. Documented positive T315I mutation
   E. A diagnosis of **Accelerated Phase-Chronic Myeloid Leukemia (AP-CML), Blast Phase-Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL); AND**
1. Provider attestation that all other TKIs used to treat AP-CML, BP-CML, or Ph+ALL (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) have been ineffective, not tolerated, contraindicated or not indicated; OR
2. Documented positive T315I mutation

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

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If this applies, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Will not be used with any other oncology therapy; AND
IV. Disease response to treatment defined by stabilization of disease or decrease in rate of disease progression.

Supporting Evidence

I. Ponatinib (Iclusig) is an oral tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in around 20% of patients with tyrosine kinase inhibitor-resistant disease.
II. Ponatinib (Iclusig) carries three FDA approved indications and is used in the treatment of patients with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors, accelerated phase (AP) or blast phase (BP) CML, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated, and T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.
III. The original FDA approval for ponatinib (Iclusig) took place in 2012 and was based on the PACE clinical trial which evaluated safety and efficacy of ponatinib (Iclusig). Post-marketing studies submitted to the FDA included a 5 year follow up PACE study and an ongoing OPTIC clinical trial, which informed of the optimal dosing in patients with CP-CML.
IV. The PACE clinical trial was an open label, single arm, phase II study in adult subjects with CML (all phases) or Ph+ ALL with resistance/intolerance to dasatinib or nilotinib, or development of T315I mutation after tyrosine kinase inhibitor (TKI) therapy. There were 270 subjects in CP-CML, 85 subjects in AP-CML, 62 subjects in BP-CML, and 62 subjects in Ph+ALL. These subjects were further randomized based on T315I mutation status. Nearly one-third of subjects (29%) had the T315I mutation. The primary efficacy endpoint of major cytogenic response (MCyR) by 12 months of treatment was met in 51% of those with resistance or intolerance to prior TKI therapy and in 70% of those with a positive T315I mutation status in the CP-CML cohort. In AP-CML, BP-CML, and Ph+ALL the primary endpoint was major hematologic response (MaHR) by 6 months of treatment which was met in 57% of those with prior resistance or intolerance to TKI therapy and in 50% of those with a positive T315I mutation status in the AP-CML cohort. MaHR was met in
35% of those with resistance or intolerance to prior TKI therapy and in 33% of those with a positive T315I mutation status in the BP-CML/Ph+ALL cohort.

V. The five year follow up study of ponatinib (Iclusig) demonstrated a continued clinical benefit in patients with heavily treated CML or Ph+ALL. The types of adverse events reported were generally similar to those reported previously and included rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), and constipation (41%). Dose related adverse events included cardiovascular, cerebrovascular, and peripheral vascular events. The cumulative incidence of arterial occlusive events (AOEs) was 25% in the overall population (serious AOE, 20%) and 31% in the CP-CML population (serious AOE, 26%); higher cumulative incidence in CP-CML correlates with the longer duration of treatment.

VI. OPTIC is an ongoing phase 2, open label, randomized, multicenter clinical trial evaluating response-based dosing regimens of ponatinib (Iclusig) with the aim of optimizing its efficacy and safety in patients with CP-CML who are resistant or intolerant to prior TKI therapy. Interim results at 21 months of follow up show benefit of ponatinib (Iclusig) in all three dosing regimens studied (15 mg, 30 mg, and 45 mg), with the 45 mg starting dose showing greatest efficacy results. Thus far, the FDA has made recommendations to start with the 45 mg dose which could subsequently be titrated down to 15 mg upon achievement of <1% BCR-ABL1. Primary analysis will provide a refined understanding of the benefit: risk profile of three different starting doses of ponatinib (Iclusig).

VII. For the treatment of Ph+ALL, current NCCN guidelines recommend dasatinib (Sprycel) and imatinib (Gleevec) as the preferred agents as well as other TKIs such as bosutinib (Bosulif), nilotinib (Tasigna), or ponatinib (Iclusig). Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.

VIII. For the treatment of CP-CML, current NCCN guidelines recommend the following agents depending on the patient’s risk score and mutation profile: imatinib (Gleevec), bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) when there’s resistance to two prior TKIs. For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) with omacetaxine (Synribo) cited as being useful in certain circumstances.

Investigational or Not Medically Necessary Uses

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

A. Newly diagnosed CP-CML

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

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


Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy criteria transitioned to a new format; criteria changes include the removal of laboratory monitoring requirements (blood counts, hepatic enzyme tests, serum lipase) and monitoring of atrial thrombotic events, addition of a new dosage forms 10 mg and 30 mg tablets, and addition of requiring two prior TKIs in CP-CML, consistent with the FDA labeling change.</td>
<td>03/2021</td>
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<td>Policy criteria created</td>
<td>05/2013</td>
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</table>
Pralsetinib (Gavreto™)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP220

Split Fill Management*

Description
Pralsetinib (Gavreto) is an orally administered kinase inhibitor of RET.

Length of Authorization
- N/A

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tbody>
<tr>
<td>pralsetinib (Gavreto)</td>
<td>100 mg capsules</td>
<td>RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory</td>
<td>120 capsules/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. **Pralsetinib (Gavreto)** is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Pralsetinib (Gavreto) is the second FDA-approved RET-targeted therapy, joining selpercatinib (Retevmo).

II. RET fusion-positive NSCLC, advanced or metastatic: First-line treatments include cabozantinib (Cometiq®) or vandetanib (Caprelsa®) (both off-label for lung cancer), combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed (Alimta®), and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine); however, all of these therapies show poorer outcomes in this population vs. non-RET mutated NSCLC.

- NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy after other options have failed (recommendation
Category 2a). Cabozantinib (Cometriq) and vandetanib (Caprelsa) are listed as useful in certain circumstances, with a Category 2a and 2b recommendation, respectively. ESMO guidelines mention pralsetinib (Gavreto) and selpercatinib (Retevmo) for RET-mutated NSCLC; however, given the limited data, enrollment in clinical trials is encouraged.

III. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).
   - NCCN guidelines recommend cabozantinib (Cometriq) and vandetanib (Caprelsa) as Category 1 preferred options. Selpercatinib (Retevmo) is listed as a Category 2a preferred therapy for those with RET-mutations in both the locoregional, symptomatic, and unresectable setting, as well as the recurrent or persistent settings. Enrollment in clinical trials has a Category 2a recommendation.

IV. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic MTC, RAI is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).
   - NCCN guidelines recommend lenvatinib (Lenvima) and sorafenib (Nexavar) as Category 2a with lenvatinib (Lenvima) preferred. Selpercatinib (Retevmo) is the preferred therapy for RET fusion-positive disease, Category 2a.

V. Pralsetinib (Gavreto) has not been included in treatment guidelines for thyroid cancer.

VI. Pralsetinib (Gavreto) is being evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). These indications were approved under the accelerated pathway and continued approval may be contingent upon verification of clinical benefit in confirmatory trials. The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.

VII. For RET fusion-positive NSCLC: Patients were advanced or metastatic and were either treatment naïve or progressed on platinum-based chemotherapy. For RET-mutant MTC, patients were either treatment naïve or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa). All patients had progressed on standard of care for RET-fusion-positive TC.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RET Fusion+ NSCLC (n=87)</th>
<th>RET-Mutant MTC (n=55)</th>
<th>RET Fusion-Positive TC (n=9)</th>
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</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>57% (46, 68)</td>
<td>60% (46, 73)</td>
<td>89% (52, 100)</td>
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<tr>
<td>CR (%)</td>
<td>5.7%</td>
<td>1.8%</td>
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<tr>
<td>PR (%)</td>
<td>52%</td>
<td>58%</td>
<td>89%</td>
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<tr>
<td>DoR (mo)</td>
<td>NR (15.2-NE)</td>
<td>NR (15.1, NE)</td>
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<td>DoR ≥ 6 mo (%)</td>
<td>80%</td>
<td>79%</td>
<td>100%</td>
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<table>
<thead>
<tr>
<th>Outcome</th>
<th>RET Fusion+ NSCLC (n=27)</th>
<th>RET-Mutant MTC (n=29)</th>
<th>RET Fusion-Positive TC*</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>70% (50, 86)</td>
<td>66% (46, 82)</td>
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<tr>
<td>CR (%)</td>
<td>11%</td>
<td>10%</td>
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<tr>
<td>PR (%)</td>
<td>59%</td>
<td>55%</td>
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<tr>
<td>DoR (mo)</td>
<td>9 (6.3-NE)</td>
<td>NR (NE, NE)</td>
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<td>DoR ≥ 6 mo (%)</td>
<td>58%</td>
<td>84%</td>
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</table>

*All patients were refractory to standard therapy.

VIII. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.
IX. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of 2024.

X. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain, hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

XI. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

XII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

* 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


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.
Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>02/2021</td>
</tr>
</tbody>
</table>
Pretomanid
UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP080

Description
Pretomanid is an orally administered nitroimidazooxazines antimycobacterial agent.

Length of Authorization
- Initial: six months
- Renewal: N/A

Quantity limits

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

Initial Evaluation

I. Pretomanid may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; AND
   B. The medication is prescribed by, or in consultation with a pulmonologist or infectious disease specialist; AND
   C. A diagnosis of pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) when the following are met:
      1. Documentation of resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial (e.g., amikacin, kanamycin, or capreomycin); AND
      2. Documentation of intolerance to para-aminosalicyclic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones; AND
      3. The member will be using pretomanid in combination with bedaquiline (Situro) AND linezolid (Zyvox) for the duration of therapy; AND
      4. The member will have directly observed treatment (DOT) plan in place

II. Pretomanid is considered investigational when used for all other conditions, including but not limited to:
   A. The use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox)
   B. Drug-sensitive (DS) tuberculosis
   C. Latent infection due to Mycobacterium tuberculosis
   D. Extra-pulmonary infection due to Mycobacterium tuberculosis

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.

September 01, 2022
E. Multidrug-resistant tuberculosis that is not treatment-intolerant or nonresponsive to standard therapy

Supporting Evidence

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

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

II. The primary efficacy outcome was the incidence of bacteriologic failure, relapse, or clinical failure through follow up until six months after the end of treatment; of the 107 patients assessed, 12 (11%) patients were classified as treatment failure, while 95 (89%) patients were classified as treatment success. Treatment success was defined as culture negative status at six months post treatment.

III. No pediatric patients were included in the trial.

IV. Pretomanid was only studied in combination with bedaquiline (Situro) and linezolid (Zyvox).

V. Patients that were included in the trial demonstrated resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial, and had intolerance to para-aminosalicylic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones.

Investigational or Not Medically Necessary Uses

I. Safety and efficacy has not been established for the use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox).

II. Pretomanid was FDA-approved on an accelerated approval pathway under the Limited Population Pathway for Antibacterial and Antifungal Drugs. As stated in the label, the approval of this indication is based on limited clinical safety and efficacy data. Therefore, the use of this drug is indicated for a very specific population of patients, and antimicrobial stewardship practices should be applied when treating this population of patients. Therefore, the use of pretomanid in setting...
other than the label indication [pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)], is considered experimental and investigational.

References

3. Center for Disease Control and Prevention: Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
6. Clinicaltrial.gov

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>September 2019</th>
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<tr>
<td>Date Effective</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td></td>
</tr>
<tr>
<td>Last Reviewed</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP001

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

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>alirocumab (Praluent)</td>
<td>75 mg/mL pen injector</td>
<td>Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease</td>
<td>2 mL (2 injections)/28 days</td>
</tr>
<tr>
<td></td>
<td>150 mg/mL pen injector</td>
<td></td>
<td></td>
</tr>
<tr>
<td>evolocumab (Repatha)</td>
<td>140 mg/mL auto injector; prefilled syringe</td>
<td></td>
<td>2 mL (2 injections)/28 days</td>
</tr>
<tr>
<td></td>
<td>420 mg/mL solution cartridge</td>
<td></td>
<td>3.5 mL (1 injection)/28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

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

E. A diagnosis of one of the following:

1. **Atherosclerotic cardiovascular disease (ASCVD); AND**
   
i. Member is 18 years of age or older; **AND**
   
   ii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **OR**
       
       a. Ezetimibe (Zetia) would not be an effective therapy based on LDL-C goal and current LDL-C (documentation is verified by a clinical pharmacist at the health plan); **AND**
   
   iii. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
   
   iv. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **OR**

2. **Heterozygous familial hypercholesterolemia; AND**
   
i. The member is 18 years of age or older; **OR**
   
   a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
   
   ii. Diagnosis of heterozygous familial hypercholesterolemia is confirmed by one of the following
       
       a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score greater than 8)

       b. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **OR**

3. **Homozygous familial hypercholesterolemia; AND**
   
i. The member is 18 years of age or older; **OR**
   
   a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
   
   ii. The member has a history of an untreated LDL-cholesterol level greater than 500 mg/dL with either evidence of heterozygous familial hypercholesterolemia in both parents or xanthoma before the age of 10; **OR**
   
       a. DNA mutation analysis supporting the diagnosis of homozygous familial hypercholesterolemia (e.g, *LDLR*, *APOB*, *PSCK9*, *LDLRAP1*); **AND**
   
   iii. Evolocumab (Repatha) or alirocumab (Praluent) will not be used in combination with lopitamide (Juxtapid)

II. **Alirocumab (Praluent) or evolocumab (Repatha) are considered not medically necessary when used for all other conditions, including but not limited to:**

   A. Hypercholesterolemia non-familial cause
III. Alirocumab (Praluent) or evolocumab (Repatha) are considered **investigational** when used for all other conditions, including but **not limited to**:
   A. ASCVD primary prevention in non-familial hypercholesterolemia

**Renewal Evaluation**

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

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

III. Member has experienced a decrease from baseline LDL-C while on therapy

**Supporting Evidence**

I. Alirocumab (Praluent) is FDA-approved to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease and as an adjunct to diet, alone, or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

II. Evolocumab (Repatha) is FDA-approved to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

III. The 2017 American Association of Clinical Endocrinologists (AACE) guidelines state statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. Additionally, guidelines state PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.

IV. Seventy to ninety percent of patients are able to tolerate an alternate long-term statin. In clinical practice, 10-25% of patients have musculoskeletal adverse events associated with statin use; however, several studies have determined that the majority of patients with statin-associated muscle symptoms are able to tolerate subsequent statin therapy with modified dosing regimens.

V. The 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define ineffective therapy as inability to achieve an LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.

VI. **Atherosclerotic cardiovascular disease (ASCVD)**: 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines recommend patients with clinical ASCVD reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. In
patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions).

- The 2017 American College of Cardiology (ACC) Recommendations for Non-Statin Therapy recommends consideration of adding ezetimibe first in patients that are statin intolerant with clinical ASCVD and may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.

- Ezetimibe is a clinically appropriate and cost-effective alternative to PSCK9 inhibitors in scenarios where addition of ezetimibe would be expected to bring LDL-C levels to a patient specific LDL-C goal. In patients with ASCVD, the 2018 AHA/ACC Cholesterol Guidelines recommend achieving a ≥50% reduction in LDL-C levels and an LDL-C goal of <70mg/dL. The 2021 European Society of Cardiology Guidelines recommend lipid-lowering treatment with an ultimate goal of <55mg/dL and a ≥50% reduction of LDL-C from baseline. Depending on specific risk factors, providers may choose different LDL-C goals for their patients. Ezetimibe is cited to lower LDL-C by 15-20% when used by itself or in combination with a statin. Therefore, information about patient’s specific LDL-C goals and concomitant cholesterol lowering therapies is required to estimate overall LDL-C lowering effect and assess appropriateness of treatment with ezetimibe.

- Per Schmidt et al. Cochrane Review, “In comparisons of PCSK9 inhibitors versus no PCSK9 inhibitors, current evidence suggests that PCSK9 inhibitors decrease CVD incidence without affecting the incidence of all-cause mortality. In comparisons of PCSK9 inhibitors versus alternative (more established) treatments such as statins or ezetimibe, high-quality evidence is lacking. Differences in risk between people treated with and without PCKS9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g., < 1% change in risk).”

VII. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member’s clinical profile to determine individual patient risk and treatment but should not necessarily be used alone for the purposes of clinical diagnosis.

VIII. **Heterozygous familial hypercholesterolemia**: The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria (“definite FH” using either the Simon Broome or Dutch Lipid Network).

<table>
<thead>
<tr>
<th>Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children</td>
<td>1</td>
</tr>
<tr>
<td>Tendinous xanthomata in the patient or a first-degree relative</td>
<td>2</td>
</tr>
<tr>
<td>DNA-based evidence of mutation in the LDLR, PCSK9, or APOB gene</td>
<td>6</td>
</tr>
<tr>
<td>Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative</td>
<td>3</td>
</tr>
<tr>
<td>Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative</td>
<td>4</td>
</tr>
</tbody>
</table>

A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.

### Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>• First-degree relative with known premature (men: &lt;55 years; women: &lt;60 years) coronary or vascular disease, or</td>
<td>1</td>
</tr>
<tr>
<td>• First-degree relative with known LDL-C above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td>• First-degree relative with tendinous xanthomata and/or arcus cornealis, or</td>
<td>2</td>
</tr>
<tr>
<td>• Children &lt;18 years of age with LDL-C above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
</tr>
<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) cerebral or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>• Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>• Arcus cornealis before age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>LDL-C levels</strong></td>
<td></td>
</tr>
<tr>
<td>• LDL-C ≥8.5 mmol/L (325 mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td>• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA analysis</strong></td>
<td></td>
</tr>
<tr>
<td>• Functional mutation in the LDLR, apoB, or PCSK9 gene</td>
<td>8</td>
</tr>
</tbody>
</table>

Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained)

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

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

IX. Homozygous familial hypercholesterolemia (HoFH): Evolocumab (Repatha) and alirocumab (Praluent) are FDA-approved in the setting of HoFH and includes patients ages 13 and older (Repatha) or 18 and older (Praluent). Evolocumab (Repatha) was studied in one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B) in patients greater than, or equal to, 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolemia diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL cholesterol concentration >13 mmol/L (500 mg/dL)) plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents. Alirocumab (Praluent) was studied in one randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ODYSSEY HoFH) in patients 18 years of age or older with homozygous familial hypercholesterolemia. Patients in the clinical trial had a diagnosis of familial hypercholesterolemia confirmed in the patient’s medical history by clinical diagnosis or by genotyping. The genotyping results from this study found patients had mutations in the LDLR, LDLRAP1, PCSK9, or APOB genes.
• Use of evolocumab (Repatha) and alirocumab (Praluent) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied in a large population, and the efficacy and safety is unknown. Concurrent use is considered experimental and investigational.

Investigational or Not Medically Necessary Uses

I. Primary hypercholesterolemia
   A. The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines.
   B. 2018 AHA/ACC guidelines state “at any given price, the economic value of PCSK9 inhibitors will be improved by restricting their use to patients at very high-risk of ASCVD events”.

II. ASCVD primary prevention in non-familial hypercholesterolemia
   A. Trials in prevention of cardiovascular events have occurred in the established cardiovascular disease population (secondary prevention). PCSK9 inhibitors have not been adequately evaluated in primary prevention in patients without familial hypercholesterolemia. Applicability of results to primary prevention is limited.
   B. Per 2018 AHA/ACC guidelines, among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices. Economic models have not been produced for primary prevention in non-familial hypercholesterolemia.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added criteria allowing a path to coverage in scenarios where ezetimibe would not be expected to bring LDL-C levels to a desired LDL-C goal. Updated supporting evidence.</td>
<td>08/2022</td>
</tr>
<tr>
<td>Updated to include age expansion in pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C</td>
<td>02/2022</td>
</tr>
<tr>
<td>Added new FDA-approved indication of HoFH for Praluent. Updated diagnosis confirmation requirements for HeFH and HoFH to align with current guidelines. Removed statement around combination use with Kynamro as product has been discontinued. Update to supporting evidence.</td>
<td>04/2021</td>
</tr>
<tr>
<td>Review. Update to supporting evidence</td>
<td>12/2020</td>
</tr>
<tr>
<td>Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.</td>
<td>06/2019</td>
</tr>
<tr>
<td>Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.</td>
<td>11/2018</td>
</tr>
<tr>
<td>Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to &gt;70 for all indications. Increased initial authorization to 12 months. Removed requirement to try and fail statin plus Zetia combination therapy. Removed DNA mutation analysis confirming homozygous familial</td>
<td>06/2018</td>
</tr>
</tbody>
</table>

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hypercholesterolemia diagnosis. Required trial and failure of high intensity statin for a minimum of 8 week duration. Updated renewal criteria to assess overall reduction in LDL rather than specific percent reduction.

<table>
<thead>
<tr>
<th>Previous review</th>
<th>11/2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.</td>
<td>02/2016</td>
</tr>
<tr>
<td>Criteria created</td>
<td>08/2015</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP145

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

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

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

Length of Authorization
- Initial:
  - Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), and macitentan (Opsumit): Three months
  - Riociguat (Adempas), iloprost (Ventavis), treprostinil inhalation (Tyvaso), treprostinil tablet (Orenitram), treprostinil injection (Remodulin) and selexipag (Uptravi): 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ambrisentan (Letairis)</td>
<td>5 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>generic ambrisentan</td>
<td>5 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bosentan (Tracleer)</td>
<td>32 mg tablet for oral suspension</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>120 tablets/30 days</td>
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<tr>
<td></td>
<td>62.5 mg film-coated tablet</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>125 mg film-coated tablet</td>
<td></td>
<td></td>
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<tr>
<td>generic bosentan</td>
<td>32 mg tablet for oral suspension</td>
<td></td>
<td>120 tablets/30 days</td>
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<td></td>
<td>62.5 mg film-coated tablet</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>125 mg film-coated tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macitentan (Opsumit)</td>
<td>10 mg tablet</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage Form</th>
<th>Indications</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>riociguat (Adempas)</td>
<td>0.5 mg tablets</td>
<td>Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)</td>
<td>90 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>1 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iloprost (Ventavis)</td>
<td>10 mcg/mL inhalation solution ampule</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>9 cartons of 30 ampules per 30 day supply</td>
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<tr>
<td></td>
<td>20 mcg/mL inhalation solution ampule</td>
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<td></td>
</tr>
<tr>
<td>treprostinil (Tyvaso)</td>
<td>1.74 mg/2.9 mL inhalation solution ampule</td>
<td>Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)</td>
<td>1 Inhalation System Starter Kit (28 ampule carton)/ 1st 28 days of initiation therapy</td>
</tr>
<tr>
<td></td>
<td>5 mg/mL injection solution</td>
<td></td>
<td>1 Inhalation System Refill Kit (28 ampule carton)/28 days</td>
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<tr>
<td></td>
<td>10 mg/mL injection solution</td>
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<td>7 Four Pack Cartons with one foil pouch containing four 2.9 mL ampules/28 days</td>
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<td>20 mg/20 mL injection solution</td>
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<tr>
<td>treprostinil (Remodulin)</td>
<td>0.125 mg ER tablet</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>up to 50 ng per kg per minute subcutaneously or intravenously</td>
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<td>0.25 mg ER tablet</td>
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<td>5 mg ER tablet</td>
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<td>treprostinil (Orenitram)</td>
<td>200 mcg</td>
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<td>90 extended-release oral tablets/30 days</td>
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<td>400 mcg</td>
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</tr>
<tr>
<td></td>
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</table>

**Initial Evaluation**

I. Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso)
inhalation solution, treprostinil (Orenitram), treprostinil injection (Remodulin), and selexipag (Uptravi) may be considered medically necessary when the following criteria below are met:

A. Member is 18 years of age or older; OR
   1. Member is three years of age or older and request is for bosentan (generic, Tracleer); AND
B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; AND
C. A diagnosis of one of the following:
   1. Pulmonary arterial hypertension (PAH) (WHO) Group 1 with WHO Functional Class II-IV symptoms; AND
      a. An acute vasoreactivity test has been performed; AND
         i. Results were negative; OR
         ii. Results were positive; AND
            a) Treatment with a calcium channel blocker (CCB) (e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, or verapamil) has been ineffective after three months of therapy, unless contraindicated, or not tolerated; AND
            b. Treatment with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily] has been ineffective after three months of therapy, contraindicated, or not tolerated; OR
               i. The request is for generic ambrisentan in combination with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily]; AND
      c. The request is for generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas); OR
      d. The request is for brand ambrisentan (Letairis); AND
         i. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; OR
      e. The request is for brand bosentan (Tracleer); AND
         i. Generic bosentan has been ineffective, contraindicated, or not tolerated; OR
      f. The request is for iloprost (Ventavis) inhalation solution or treprostinil (Tyvaso) inhalation solution; AND
         i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contrainedicated, or not tolerated; OR
      g. The request is for treprostinil (Orenitram) or selexipag (Uptravi); AND
         i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; OR
      h. The request is for generic treprostinil injection solution (generic Remodulin); OR
         1) The request is for brand Remodulin and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; AND

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i. Member has WHO Class IV symptoms or is classified as high risk (poor prognosis) [see appendix table 1]; OR

ii. The member is classified as low risk (good prognosis); AND
   2) Treatment with an ERA (e.g., bosentan, ambrisentan), AND either a PDE5 inhibitor (e.g., sildenafil, tadalafil) OR Adempas (riociguat) has been ineffective, contraindicated, or not tolerated; OR

iii. Member is transitioning from epoprostenol to treprostinil (Remodulin)

2. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4); AND
   i. Member has inoperable CTEPH; OR
   ii. Member had a surgery for CTEPH performed; AND
   iii. The request is for riociguat (Adempas); OR

3. Pulmonary Hypertension (PH) Due to Interstitial Lung Disease (ILD) (WHO Group 3); AND
   i. Diagnosis confirmed with chest high-resolution computed tomography (HRCT) imaging; AND
   ii. Diagnosis confirmed with a right heart catheterization (RHC); AND
   iii. Member does NOT have PH caused by obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) or hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation); AND
   iv. The request is for treprostinil (Tyvaso)

II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   B. Digital ulcers in systemic sclerosis
   C. Lowering Portal Pressure in Patients with Liver Cirrhosis
   D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
   E. Sarcoidosis

III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic obstructive pulmonary disease - Pulmonary hypertension
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)
   C. Digital ulcers in systemic sclerosis
   D. Essential hypertension
   E. Raynaud phenomenon in systemic sclerosis
   F. Thromboembolic pulmonary hypertension, chronic
IV. Macitentan (Opsumit) is considered **investigational** when used for all other conditions including but not limited to:
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   B. Digital ulcers in systemic sclerosis
   C. Glioblastoma

V. Riociguat (Adempas) is considered **investigational** when used for all other conditions including but not limited to:
   A. Systemic sclerosis-associated digital ulcers

VI. Treprostinil (Tyvaso) is considered **investigational** when used for all other conditions including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V
      • Group II - Left heart disease, including congestive heart failure (CHF)
      • Group III – Chronic obstructive pulmonary disease (COPD), bronchiectasis; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
      • Group IV - Chronic thrombotic and/or embolic disease
      • Group V - Sarcoidosis
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)

VII. Iloprost (Ventavis), treprostinil (Orenitram, Remodulin) and selexipag (Uptravi) are considered **investigational** when used for all other conditions, including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V
      • Group II - Left heart disease, including congestive heart failure (CHF)
      • Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
      • Group IV - Chronic thrombotic and/or embolic disease
      • Group V – Sarcoidosis
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)

**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**

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III. Member has exhibited improvement or stability of disease symptoms (e.g. improved exercise capacity and tolerance, reduced number of hospitalizations, improvement in WHO functional class).

Supporting Evidence

I. Patients with PH are classified into five clinical groups based on cause of PH.
   a. Group 1: pulmonary arterial hypertension (PAH) which has several causes (e.g., inheritable causes, drugs, connective tissue disease)
   b. Group 2: PH due to left-sided heart disease
   c. Group 3: PH due to chronic lung disorders and hypoxemia
   d. Group 4: PH due to pulmonary artery obstructions
   e. Group 5: PH due to unidentified mechanisms

II. The safety and efficacy of bosentan (Tracleer) in pediatric patients was evaluated in an open-label, uncontrolled study with 19 pediatric PAH patients aged 3 to 15 years. Patients had primary pulmonary hypertension \( n = 10 \) or PAH related to congenital heart diseases \( 9 \) patients and were WHO functional class II or class III at baseline. Patients were dosed with bosentan for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. Hemodynamics were measured in 17 patients. The mean decrease in (pulmonary vascular resistance) PVR was \( 389 \text{ dyn·sec·cm}^{-5} \), which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.

*Normal PVR value is \( <250 \text{ dyn·sec·cm}^{-5} \) but PAH patients, depending on the severity of the disease state, have a significantly higher PVR value. A Systematic Review and Meta-Analysis of 12 studies was done and baseline PVR value of the PAH patients included in the study was \( 668.6±219.1 <250 \text{ dyn·sec·cm}^{-5} \).

III. Clinical studies of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) did not include patients younger than 18 years to determine whether they respond differently from older patients. Safety and efficacy in pediatric patients has not been established.

IV. PH is a progressive and life-threatening disease. The medications as well as the disease state should be managed by a specialist.

PAH

V. The American College of Chest Physicians (CHEST) guideline for Therapy for PAH in adults suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a medical center with experience in the performance and interpretation of vasoreactivity testing. Contraindications to acute vasoreactivity testing include a low systemic BP, low CO, or the presence of FC IV symptoms. Patients who demonstrate acute vasoreactivity – in the absence of right-sided heart failure or contraindications to CCB therapy – according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB. CCBs are considered primary therapy.

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September 01, 2022
VI. Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, there is insufficient evidence to determine if one agent is superior to another.

VII. Ambrisentan (Letairis), bosentan (Tracleer), and macitentan (Opsumit) are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and decrease clinical worsening.
   a. Studies with bosentan (Tracleer) establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). The primary study endpoint was 6-minute walk distance; however, symptoms and functional status was also assessed. In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment and fully developed by about 2 months of treatment.
   b. Ambrisentan (Letairis) and macitentan (Opsumit) effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients who were included in this study had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), or PAH caused by congenital heart disease with repaired shunts (8%). The primary study endpoint was a 6-minute walk distance. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment.
   c. Macitentan (Opsumit) effect on progression of PAH was demonstrated in a multi-center, long-term, placebo-controlled study in 742 patients with symptomatic PAH WHO FC II-IV. The primary study endpoints were time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy), lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or “other worsening of PAH” during double-blind treatment plus 7 days. Other worsening was defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO FC), and need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. Treatment with OPSUMIT 10 mg resulted in a 45% reduction in the occurrence of the primary endpoint.

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orentram), treprostinil (Remodulin), and selexipag (Upravi) are synthetic analogs of prostacyclin indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (WHO Class), and lack of deterioration. Injectable treprostinil (Remodulin) also carries FDA approval for transition from epoprostenol.

IX. Studies in Iloprost (Ventavis) establishing effectiveness included predominately patients with WHO Functional Class III-IV symptoms, etiologies of idiopathic or heritable PAH (65%), or PAH associated with connective tissue diseases (23%). The primary efficacy endpoint was clinical response at 12 weeks with a composite endpoint defined by: improvement in exercise ability (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing.
improvement with at least one WHO FC versus baseline, and no death or deterioration of pulmonary hypertension. The percentage of patients who had a minimum increase of at least 10 percent in the distance walked within six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group. The absolute change in the 6MWD was significantly larger in the iloprost group. More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the WHO FC.

X. Studies in treprostinil (Tyvaso) to establish effectiveness included predominately patients with WHO Functional Class III symptoms, etiologies of idiopathic or heritable PAH (56%), or PAH associated with connective tissue diseases (33%). While there is long-term data on use of treprostinil (Tyvaso) by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil (Tyvaso) has been on a background of bosentan (Tracleer) (an endothelin receptor antagonist) or sildenafil (Revatio) (a phosphodiesterase type 5 inhibitor).

XI. Per the package insert, the study in treprostinil (Orenitram), that established effectiveness included predominately patients with WHO functional class II-III symptoms, etiologies of idiopathic or heritable PAH (75%), or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of treprostinil (Orenitram) on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

XII. Treprostinil injection (Remodulin) is indicated for subcutaneous or intravenous use only as a continuous infusion. The package insert states treprostinil injection is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated. Treprostinil can be self-administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. 2019 CHEST guidelines recommend use of treprostinil injection (Remodulin) for patients with continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents; or in patients with WHO functional class IV.

XIII. Effectiveness of selexipag (Uptravi) was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

XIV. ACCF/AHA guidelines indicate oral ERA or PDE-5 inhibitor therapy as first line treatment for lower risk PAH patients. There is insufficient safety and efficacy evidence to establish that any one oral therapy for PAH is clearly superior to another. Treatment guidelines do support combination therapy of PDE, ERA, and prostanoid agents.

XV. For patients with WHO functional class II or III 2019 CHEST guidelines recommend the combination of ambrisentan and tadalafil as first line therapy. This is based on data from the AMBITION trial. The trial involved 605 patients with WHO functional class II or III PAH. Patients were randomly assigned to receive once-daily ambrisentan plus tadalafil or to either drug alone. Doses were titrated from 5-10 mg/day for ambrisentan and from 20-40 mg/day for tadalafil. Treatment with the combination was associated with an approximately 50% reduction in risk for clinical failure compared with either drug alone (P = .0002), with improved exercise ability as well as decreased disease progression and hospitalization.
XVI. Due to the lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and their differing burdens and risks to patients, CHEST guidelines recommend that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not yet been studied; therefore, all treatment decisions should be informed by patient preferences, goals, and assessments of health-related quality of life.

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

**PH due to ILD**

XVII. WHO Group 3 PH can be further broken down to specific causes. Those causes are:
- Obstructive lung disease (e.g., COPD or bronchiectasis)
- Restrictive lung disease (e.g., ILD, kyphoscoliosis)
  - Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema)
- Hypoxia without lung disease (e.g., high altitude, sleep apnea, obesity hypoventilation)
- Developmental lung disorders (e.g., bronchopulmonary dysplasia, congenital lobar emphysema)

XVIII. FDA approval for treprostinil (Tyvaso) is specific to PH associated with ILD as that was the population evaluated in clinical trials.

XIX. The safety and efficacy of treprostinil (Tyvaso) inhalation solution for the treatment of patients with PH due to ILD was studied in a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled trial.

a. Patients were adults with Group 3 pulmonary hypertension diagnosed by right heart catheterization. The mean age was 66.5 years, 46.9% were female and majority had the diagnosis of idiopathic interstitial pneumonia (in 44.8%).

b. Primary efficacy outcome measure of difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16 was met with a difference of 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001).

c. Clinical worsening was evaluated as a secondary endpoint and occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test)

d. There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16

e. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo.
XX. Patients who have shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy were excluded from the clinical trial. There is a lack of clinical trial data to show that Treprostinil (Tyvaso) would be effective or safe in this patient population.

**Investigational Uses**

I. Ambrisentan (generic, Letairis);
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
      a. AMBER I is a phase 3, randomized, double-blind, placebo controlled, parallel group, 16-week study evaluating the safety and efficacy of ambrisentan and placebo in subjects with inoperable CTEPH. AMBER II is an open-label, extension study of the long-term safety, tolerability, and efficacy.
      b. These studies were terminated early due to futility of enrollment. This was due to several factors, including an unexpectedly low screening rate (~20% of expected) and high screening failure rate (approaching 60%, mostly due to concerns regarding inoperability raised by the central adjudication committee).
   B. Digital ulcers (DU) in systemic sclerosis
      a. A pilot study was conducted to evaluate the efficacy of ambrisentan in the treatment and prevention of digital ulcers in patients with systemic sclerosis and they found that ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs. There is no robust data to support the use of ambrisentan in DUs.
   C. Lowering Portal Pressure in Patients with Liver Cirrhosis
      a. A phase II, single-arm, open-label study to characterise the effect on portal pressure, the effect on renal function and the pharmacokinetic profile of ambrisentan in patients with decompensated cirrhosis is being conducted but no results have been published yet.
   D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
      a. A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy and safety of ambrisentan in subjects with idiopathic pulmonary fibrosis and pulmonary hypertension called ARTEMIS-PH was terminated.
   E. Sarcoidosis
      a. Ambrisentan was studied for Sarcoidosis Associated Pulmonary Hypertension in a single group assignment, open-label clinical trial and suggested a possible benefit of this drug in selected patients. However, the study was a prospective, open-label, proof of concept trial of ambrisentan that wasn’t powered enough to show robust safety and efficacy data to support the use.
      b. There is limited or no published clinical trial data to support the use of ambrisentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that...
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II. Bosentan (Tracleer)
   A. Chronic obstructive pulmonary disease - Pulmonary hypertension
      a. In a 12-week randomized trial (N=30) in patients with severe, or very severe, COPD who did not have severe pulmonary hypertension at rest, there was no significant between-group difference in change from baseline in the mean 6-minute walking distance. Additionally, from baseline to week 12, the mean arterial partial pressure of oxygen significantly decreased in the bosentan group compared with placebo. Health-related quality of life scores (Short-Form-36 Health Survey) also significantly worsened in the bosentan group compared with placebo.
      b. In a small, open-label study (N=32), addition of bosentan to best supportive care (BSC) improved the 6-minute walking distance and WHO functional class compared with patients receiving BSC alone. Bosentan plus BSC did not significantly improve baseline pulmonary volumes (functional vital capacity, forced expired volume in 1 second), cardiac index, arterial blood gases (partial pressure of oxygen and carbon dioxide), or quality of life (St. George questionnaire).
      c. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline does not recommend use of bosentan for treating patients with severe COPD.
   B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
      a. Bosentan was studied in a prospective, phase III, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability in 157 patients with inoperable CTEPH (NCT00313222). The primary outcome was change from baseline to week 16 in 6MWD and change from baseline to week 16 in pulmonary vascular resistance (PVR) at rest. A statistically significant treatment effect (TE) on PVR was demonstrated: -24.1% of baseline (95% confidence interval [CI]: -31.5% to -16.0%; p < 0.0001). Mean TE on 6-min walk distance was +2.2 m (95% CI: -22.5 to 26.8 m; p = 0.5449) which is not statistically significant.
      b. The BENEFIT open-label, extension study in patients with inoperable CTEPH. In total, 148 of the patients who received randomized treatment rolled over into the extension. The trial data has not been published.
      c. There is limited clinical trial data to support the use of bosentan in CTEPH. The clinical trial showed very limited efficacy and safety data.
   C. Digital ulcers in systemic sclerosis
      A. In a double-blind, placebo-controlled study, 122 patients with limited or diffuse systemic sclerosis, according to American College of Rheumatology criteria, and documented digital ulcer within the previous 12 months were randomized 2:1 to treatment with oral bosentan (79 patients) or placebo (43 patients). Mean patient age was 51.8 years, and 63% of patients had digital ulcers at baseline. In patients receiving bosentan, the number of new digital ulcers was significantly reduced compared with placebo (P=0.0083), averaging 1.4 and 2.7 new ulcers per patient, respectively. Of patients with digital ulcers at baseline, an average of 1.8 new ulcers occurred per...
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D. Essential hypertension
   a. There is no evidence that differentiates safety and efficacy of bosentan from other traditional medications (diuretics, CCB, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and alfa and beta blockers).

E. Raynaud phenomenon in systemic sclerosis
   a. Data from controlled and uncontrolled trials evaluating bosentan (Tracleer) in the management of secondary Raynaud phenomenon demonstrate conflicting results in clinical and microvascular assessments. According to evidence-based international consensus-derived recommendations, bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, and should be considered after other therapies have failed.

F. Thromboembolic pulmonary hypertension, chronic
   a. A systematic review identified 2 randomized trials of 182 patients with chronic thromboembolic pulmonary hypertension that compared 16 weeks of treatment with bosentan (Tracleer) versus placebo. Bosentan (Tracleer) significantly improved the cardiopulmonary hemodynamic parameters of cardiac index and pulmonary vascular resistance. Bosentan (Tracleer) did not significantly affect the 6-minute walk distance, mean pulmonary arterial pressure, risk of functional class deterioration, or risk of clinical worsening. The risk of liver function abnormality was significantly increased with bosentan (Tracleer).

III. Macitentan (Opsumit);
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
      a. The safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension were evaluated in MERIT-1 and MERIT-2:
         i. MERIT-1 is a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability in 80 patients. The primary efficacy endpoint is defined as the pulmonary vascular resistance (PVR) at rest at week 16 expressed as percent of baseline PVR at rest and the geometric mean PVR at rest decreased to 73-0%
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ii. MERIT-2 is an ongoing, long-term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess safety, tolerability and efficacy. Results from this trial have not been reported at this time.

b. There is insufficient clinical trial data to support the use of macitentan in patients with CTEPH. Clinical trials are ongoing to further evaluate macitentan for CTEPH.

B. Digital ulcers in systemic sclerosis

a. A prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis was terminated.

b. Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted in patients with systemic sclerosis and active digital ulcers at baseline. The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. The results of the studies do not support the use of macitentan for the treatment of digital ulcers in this patient population.

C. Glioblastoma

a. A single-center, open-label, phase 1 study of concurrent therapy with macitentan, radiotherapy, and temozolomide, followed by maintenance therapy with macitentan and temozolomide in subjects with newly diagnosed glioblastoma was terminated due to low recruitment.

b. A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide was terminated because the results did not clearly support continuing development in recurrent GBM.

c. There is limited or no published clinical trial data to support the use of macitentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, terminated, or data was not published.

IV. Riociguat (Adempas);

A. Systemic sclerosis-associated digital ulcers

a. Seventeen participants (eight placebo, nine riociguat) were randomized at five centers. Baseline characteristics were comparable between the treatment groups, except for participants who were randomized to placebo were older and had longer disease duration. Treatment with riociguat did not reduce the number of DU net burden compared with placebo at 16 weeks. Open-label extension suggests that longer duration is needed to promote DU healing, which needs to be confirmed in a new trial.
b. The conducted trials are not powered enough and show low or no efficacy. There is limited to no published clinical trial data to support the use of riociguat (Adempas) in conditions other than persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH).

VIII. Treprostinil (Tyvaso);
A. Pulmonary hypertension (PH) WHO Groups II-V
   • Group II - Left heart disease, including congestive heart failure (CHF)
   • Group III – Non-ILD lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis; Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
   • Group IV - Chronic thrombotic and/or embolic disease
   • Group V - Sarcoidosis

There is limited or no published clinical trial data to support the use of treprostinil (Tyvaso) in conditions other than PAH and PH due to ILD. The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IX. Iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi);
A. Pulmonary hypertension (PH) WHO Groups II-V
   • Group II - Left heart disease, including congestive heart failure (CHF)
   • Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
   • Group IV - Chronic thrombotic and/or embolic disease
   • Group V - Sarcoidosis

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

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);
A. Chronic thromboembolic pulmonary hypertension (CTEPH) – WHO Group IV
   a. There is insufficient data to support the use of selexipag (Uptravi) in patients with inoperable or persistent/recurrent after surgical and/or interventional treatment CTEPH. Clinical trials are ongoing, and results are not yet available.
   b. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

Appendix

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September 01, 2022
I. Table 1: PAH Determinants of Prognosis (ACCF/AHA Guidelines)

<table>
<thead>
<tr>
<th>Determinants of Risk</th>
<th>Lower Risk (Good Prognosis)</th>
<th>Higher Risk (Poor Prognosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class†</td>
<td>II, III</td>
<td>IV</td>
</tr>
<tr>
<td>6MW distance‡</td>
<td>Longer (greater than 400 m)</td>
<td>Shorter (less than 300 m)</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO2 greater than 10.4 mL/kg/min</td>
<td>Peak VO2 less than 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP less than 10 mm Hg, CI greater than 2.5 L/min/m²</td>
<td>RAP greater than 20 mm Hg, CI less than 2.0 L/min/m²</td>
</tr>
<tr>
<td>BNP§</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.

†WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.

‡6MW distance is also influenced by age, gender, and height.

§As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

References

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5. Iloprost (Ventavis®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 10/16/2017
6. Treprostinil (Tyvaso®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 03/2021
7. Treprostinil (Orenitram®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 01/24/2017
8. Selexipag (Upravi®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 09/04/2019
15. Galie, Nazzareno MD; Olschewski, Horst MD; Oudiz, Ronald J. MD; Torres, Fernando MD. Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. Circulation. 117(23), 10 June 2008. DOI: 10.1161/CIRCULATIONAHA.107.742510 PMID: 18506008
17. N. Channick MD; Marion Delcroix MD; Hossein-Ardeshir Ghofrani MD; Elke Hunsche PhD. Effect of Macitentan on Hospitalizations: Results from the SERAPHIN Trial. January 2015. 3(1). 1-8. https://doi.org/10.1016/j.jchf.2014.07.013
DOI: 10.1056/NEJMoa020204 PMID: 25457902
24. Medical University of South Carolina, Gilead Sciences. Ambrisentan (Letairis) for Sarcoidosis Associated Pulmonary Hypertension. ClinicalTrials.gov Identiﬁer: NCT00851929


37. Remodulin[treprostinil] [package insert] United Therapeutics Corp; Research Triangle Park, NC. Revised July 2018

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>• Added new indication of PH due to ILD for treprostinil (Tyvaso)</td>
<td>06/2021</td>
</tr>
<tr>
<td>• Added treprostinil injection (Remodulin) into policy</td>
<td></td>
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<tr>
<td>• Removed requirement of PDE-5 monotherapy for 3 months in those requesting generic ambrisentan in combination with a PDE-5</td>
<td></td>
</tr>
<tr>
<td>• Added requirement of prior endothelin receptor antagonist if requesting Ventavis or Tyvaso in PAH</td>
<td></td>
</tr>
<tr>
<td>• Updated renewal section with standard renewal language</td>
<td>03/2020</td>
</tr>
<tr>
<td>• Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)</td>
<td></td>
</tr>
<tr>
<td>• Updated the criteria into policy format</td>
<td></td>
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<tr>
<td>• Added acute vasoreactivity test criteria to apply to all agents</td>
<td></td>
</tr>
<tr>
<td>• Added age limit to reflect clinical trial data</td>
<td></td>
</tr>
<tr>
<td>• Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis)&amp; macitentan (Opsumit) with riociguat (Adempas) criteria and Iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi)</td>
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<tr>
<td>• Quantity limit change Iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Treprostinil (Orenitram) 5mg dosage form added</td>
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<tr>
<td>• Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option;</td>
<td></td>
</tr>
<tr>
<td>o Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated</td>
<td></td>
</tr>
<tr>
<td>o Prior to getting ambrisentan (Letairis), member has tried generic ambrisentan and treatment has been ineffective, contraindicated, or not tolerated</td>
<td></td>
</tr>
<tr>
<td>• Added generic bosentan and generic ambrisentan to the policy</td>
<td></td>
</tr>
<tr>
<td>• Added Uptravi for P&amp;T 5/4/16</td>
<td>3/29/2016</td>
</tr>
<tr>
<td>• Reviewed policy</td>
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</tr>
<tr>
<td>• Updated formatting.</td>
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<tr>
<td>• Added Tyvaso and Orenitram, removed question regarding initial 6 minute walking distance and required trial and failure of generic sildenafil only for oral prostanooid.</td>
<td>03/17/2016</td>
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<tr>
<td>• Criteria update: Validated place in therapy and recommendations.</td>
<td>03/14/2016</td>
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<tr>
<td>• Removed questions regarding contraindications, warnings/precautions.</td>
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<tr>
<td>• Updated header, footer and formatting [riociguat (Adempas)]</td>
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<tr>
<td>• Reviewed</td>
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September 01, 2022
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]</td>
<td>Prior to 3/17/2016 (no date available)</td>
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<td>Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]</td>
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<tr>
<td>Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]</td>
<td>03/2014, 03/2016</td>
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<tr>
<td>Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created</td>
<td>01/2013</td>
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pyrimethamine (Daraprim®)  
UMP POLICY

Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP234

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

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

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>Pyrimethamine (Daraprim)</td>
<td>25 mg tablets</td>
<td>Toxoplasmosis prophylaxis</td>
<td>30 tablets / 30 days</td>
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<tr>
<td></td>
<td></td>
<td>Toxoplasmosis treatment</td>
<td>30 tablets / 30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital toxoplasmosis</td>
<td>First six months: 30 tablets / 30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Last six months: 10 tablets / 30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumocystis jiroveci pneumonia prophylaxis</td>
<td>N/A</td>
</tr>
<tr>
<td>Cystoisosporiasis (isosporiasis) treatment</td>
<td>30 tablets / 30 days</td>
<td>90 tablets / 30 days</td>
<td></td>
</tr>
</tbody>
</table>
Initial Evaluation

I. **Generic or compound pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an infectious disease specialist; **AND**
   B. Treatment with pyrimethamine compound formulation (e.g., solution, suspension, capsule) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of one of the following:
      1. **Toxoplasmosis prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND**
         ii. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
         iii. Documentation that treatment with trimethoprim-sulfamethoxazole (TMP-SMX) has been ineffective, contraindicated, or not tolerated; **AND**
         iv. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      2. **Toxoplasmosis treatment**
         i. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
            a. Presence of active radiographic changes (one or more contrast-enhancing lesions, edema); **OR**
            b. Presence of clinical symptoms (e.g., fever, lymphadenopathy, chorioretinitis, headache, or motor weakness); **AND**
         ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      3. **Congenital toxoplasmosis; AND**
         i. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      4. **Pneumocystis jiroveci pneumonia (PCP) prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND**
         ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **AND**
         iii. Treatment with trimethoprim-sulfamethoxazole (TMP-SMX) has been ineffective or contraindicated; **OR**

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*September 01, 2022*
iv. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been not tolerated; **AND**
   a. Member has been re-challenged with trimethoprim- sulfamethoxazole (TMP-SMX) using a desensitization protocol, or and is still unable to tolerate; **OR**

5. **Cystisosporiasis treatment; AND**
   i. Treatment with pyrimethamine will be used in combination with leucovorin; **AND**
   ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
      a. **Oral** trimethoprim- sulfamethoxazole (TMP-SMX); **OR**
      b. **IV** trimethoprim- sulfamethoxazole (TMP-SMX); **OR**
      c. Ciprofloxacin

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

III. Pyrimethamine (Daraprim) is considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Prevention or treatment of malaria.

IV. Pyrimethamine (Daraprim) is considered **investigational** when used for all other conditions.
Renewal Evaluation

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

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

III. Member has exhibited improvement or stability of disease symptoms (e.g., CD4 count recovery, contrast-enhancing lesions, improvement in symptoms such as fever, lymphadenopathy, chorioretinitis, or headache); **AND**

IV. Request is for compound pyrimethamine; **OR**

V. If request is for generic pyrimethamine:
   a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule); **OR**

VI. If the request is for Brand Daraprim:
   a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule) or generic pyrimethamine tablets.

Supporting Evidence

I. Pyrimethamine (Daraprim) is not considered a narrow therapeutic index drug, therefore there are no foreseeable pharmacokinetic or clinical implications in transitioning a patient from an oral generic formulation to a compounded formulation.

II. There is no universal standard scale for quantifying an immunocompromised state. The National institute of Health National Cancer Institute defines immunocompromised (also called immunosuppressed) as having a weakened immune system and reduced ability to fight infections and other diseases. This may be caused by certain conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain treatments, such as biologics, corticosteroids, DMARDS, oncolytics, radiation therapy, and stem cell or organ transplant.

III. Opportunistic infections (OIs) are illnesses that occur more frequently and are more severe in people with compromised immune systems, including HIV, hematopoietic cell transplant, solid organ transplant, cancer-related immunosuppression and hematological malignancies, or taking immunosuppressive therapies. Due to the complexity of opportunistic infections, pyrimethamine needs to be prescribed by, or in consultation with, an infectious disease specialist.

IV. Initial serological screening should be performed to determine whether the member has ever been infected or is acutely or chronically infected with toxoplasmosis. *Toxoplasma*-specific IgG and IgM tests can be performed at any commercial, non-reference, or hospital-based laboratory. A positive serologic anti-toxoplasma IgG antibody test establishes that the member has been infected and is at risk of reactivation during periods of significant immunosuppression.

V. Pyrimethamine must be taken in combination with leucovorin and an antimicrobial agent due to enhanced safety and efficacy. Administration with leucovorin is recommended to reduce incidence of hematologic adverse events (myelosuppression) while taking pyrimethamine. Pyrimethamine and...
an antimicrobial agent act synergistically by inhibiting proliferation and survival through inhibiting the folate metabolic pathway.

VI. **Toxoplasmosis prophylaxis**

a. TMP-SMX should be considered first line therapy for toxoplasmosis prophylaxis. TMP-SMX also provides protection against other pathogens, including PCP, Nocardia, enteric pathogens, Plasmodium species, urinary pathogens, and some respiratory pathogens. The broader spectrum of activity of TMP-SMX is among the reasons this drug is preferred.

b. In adults and adolescents with HIV, toxoplasmosis prophylaxis should be discontinued in patients receiving ART whose CD4 counts increase to >200 cells/mm$^3$ for more than 3 months. Toxoplasmosis prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, and likelihood of development of drug-resistant pathogens.

c. There is no consensus concerning initiation and duration of toxoplasmosis prophylaxis in immunocompromised members. Regarding the incidence rate of toxoplasmosis following hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT), prophylaxis should be maintained for at least 6 months post-transplant. It should be prolonged in cases of graft-versus-host disease, prolonged neutropenia, and prolonged administration of corticosteroids.

d. In immunocompetent individuals, acute toxoplasmosis infection is usually self-limited and rarely symptomatic, although cases of severe infection due to rare Toxoplasma genotypes have been reported. Treatment for toxoplasmosis is not required for immunocompetent members who are asymptomatic or have mild, uncomplicated acute toxoplasmosis.

VII. **Toxoplasmosis treatment**

a. Toxoplasmosis therapy requires serologic anti-toxoplasma IgG detection, radiographic changes (CT or MRI with multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema), and/or presence of clinical symptoms. Common clinical manifestations include lymphadenopathy, chorioretinitis (a type of posterior uveitis), headache, confusion, and motor weakness. The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods.

b. In members with HIV, acute therapy for toxoplasmosis must be continued for at least 6 weeks. Longer courses may be necessary if clinical or radiologic disease is extensive, or response is incomplete at 6 weeks. After completion of the acute therapy, guidelines recommend members who have completed a 6-week treatment course for acute toxoplasmosis therapy should be given chronic maintenance therapy to suppress infection until immune reconstitution occurs as a consequence of antiretroviral therapy (ART). Members receiving chronic maintenance therapy for toxoplasmosis are at low risk for recurrence if they have successfully completed initial therapy, remain asymptomatic regarding signs and symptoms of toxoplasmosis, and have an increase in their CD4 counts to >200 cells/mm$^3$ after ART that is sustained for more than 6 months.

VIII. **Congenital toxoplasmosis**

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

IX. **Pneumocystis jiroveci pneumonia (PCP) prophylaxis**
   a. The preferred PCP prophylaxis regimen for HIV and immunocompromised non-HIV infected patients is TMP-SMX, because of its superior efficacy compared with aerosolized pentamidine, oral dapsone, or oral atovaquone. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution of the drug should be considered after the reaction has resolved. Oral desensitization regimens have been used successfully for HIV-infected patients with fever and rash, and similar protocols have been used in HCT recipients with a success rate of approximately 80%. Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis.
   b. PCP prophylaxis should be discontinued in adult and adolescent members who have responded to ART with an increase in CD4 counts from 200 cells/mm³ for >3 months. Discontinuation of primary PCP prophylaxis in patients with CD4 count increase to >200 cells/mm³ as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited; stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens.
   c. PCP prophylaxis and treatment with pyrimethamine is not indicated for pediatric members. TMP–SMX is a first line prophylaxis agent due to its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. Dapsone or atovaquone are second line effective and safe prophylaxis regimens available for pediatric patients unable to take TMP-SMX.

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

XI. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:
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XII. The FDA’s review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.
   a. Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
   b. In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

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

Investigational or Not Medically Necessary Uses

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

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred regimen</th>
<th>Alternative regimens</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis Prophylaxis</td>
<td>TMP-SMX 1 DS PO daily</td>
<td>• TMP-SMX 1 DS PO three times weekly, or&lt;br&gt;• TMP-SMX SS PO daily, or&lt;br&gt;• Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or&lt;br&gt;• (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, or&lt;br&gt;• Atovaquone 1500 mg PO daily, or&lt;br&gt;• (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily</td>
<td>• CD4 count &gt;200 cells/ mm³ for &gt;3 months in response to ART; or&lt;br&gt;• Can consider if CD4 count is 100-200 cells/ mm³ and HIV RNA levels remain below limits of detection for at least 3-6 months</td>
</tr>
<tr>
<td>Treating acute Toxoplasmosis*</td>
<td>Induction: Pyrimethamine 200 mg PO once, followed by dose based on body weight:&lt;br&gt;• pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)&lt;br&gt;• pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)</td>
<td>Preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine:&lt;br&gt;• Pyrimethamine (leucovorin)† plus clindamycin 600 mg IV or PO q6h + must add additional agent for PCP prophylaxis, or&lt;br&gt;• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID, or&lt;br&gt;• (Atovaquone 1500 mg PO BID + pyrimethamine (leucovorin))‡, or&lt;br&gt;• Atovaquone 1500 mg PO BID + sulfadiazine, or&lt;br&gt;• Atovaquone 1500 mg PO BID</td>
<td>• At least 6 weeks; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks&lt;br&gt;• After completion of the acute therapy, all patients should be continued on chronic maintenance therapy</td>
</tr>
<tr>
<td>Toxoplasmosis Chronic Maintenance Therapy</td>
<td>Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily</td>
<td>• Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily; or&lt;br&gt;• TMP-SMX DS 1 tablet BID, or&lt;br&gt;• TMP-SMX DS 1 tablet daily, or&lt;br&gt;• Atovaquone 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, or&lt;br&gt;• Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses), or&lt;br&gt;• Atovaquone 750–1500 mg PO BID</td>
<td>• Successfully completed initial therapy, remain asymptomatic of signs and symptoms of toxoplasmosis, and CD4 count &gt;200 cells/mm³ for &gt;6 months in response to ART</td>
</tr>
</tbody>
</table>

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

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

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

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September 01, 2022
II. Table 2. Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis in HIV-Exposed and HIV-Infected Children

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred regimen</th>
<th>Alternative regimen</th>
<th>Treatment Duration / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prophylaxis</td>
<td>TMP-SMX 150/750 mg/m² body surface area once daily by mouth</td>
<td>For Children Aged ≥1 Month: • Dapsone 2 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus • Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days</td>
<td>Primary Prophylaxis Indicated for: IgG Antibody to Toxoplasma and Severe Immunosuppression: • HIV-infected children aged &lt;6 years with CD4 percentage &lt;15%; HIV infected children aged ≥6 years with CD4 count &lt;100 cells/mm³</td>
</tr>
<tr>
<td>Secondary Prophylaxis (Suppressive Therapy)</td>
<td>• Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days</td>
<td>For Children Aged 1–3 Months and &gt;24 Months: • Atovaquone 30 mg/kg body weight by mouth once daily Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days</td>
<td>Criteria for Restarting Primary Prophylaxis: • Aged 1 to &lt;6 years with CD4 percentage &lt;15% • Aged ≥6 years with CD4 count &lt;100 to 200 cells/mm³</td>
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<td></td>
<td>• Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days</td>
<td>Acceptable Alternative Dosage Schedules for TMP-SMX: • TMP-SMX 150/750 mg/ m² body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/ m² body surface area per dose twice daily by mouth every day • TMP-SMX 75/375 mg/m² body surface area per dose twice daily by mouth TIW on alternate days</td>
<td>Criteria for Discontinuing Primary Prophylaxis: Note: Do not discontinue in children aged &lt;1 year • After ≥6 months of cART, and • Aged 1 to &lt;6 years; CD4 percentage is ≥15% for &gt;3 consecutive months • Aged ≥6 years; CD4 count &gt;200 cells/mm³ for &gt;3 consecutive months</td>
</tr>
<tr>
<td></td>
<td>• Atovaquone 30 mg/kg body weight by mouth once daily • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m² body surface area once daily by mouth</td>
<td>Children Aged 1–3 Months and &gt;24 Months: • Atovaquone 45 mg/kg body weight by mouth once daily • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m² body surface area once daily by mouth</td>
<td>Criteria for Discontinuing Secondary Prophylaxis If All of the Following Criteria are Fulfilled: • Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, and • Aged 1 to &lt;6 years; CD4 percentage ≥15% for &gt;6 consecutive months • Aged ≥6 years; CD4 cell count &gt;200 cells/mm³ for &gt;6 consecutive months</td>
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<tr>
<td></td>
<td>• Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m² body surface area once daily by mouth</td>
<td>Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX 75/375 mg/m² body surface area per dose twice daily by mouth</td>
<td>Criteria For Restarting Secondary Prophylaxis: • Aged 1 to &lt;6 years with CD4 percentage &lt;15% • Aged ≥6 years with CD4 cell count &lt;200 cells/mm³</td>
</tr>
</tbody>
</table>

*Intolerant Patients: TMP-SMX only to be used if patient intolerant to other regimens

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**Acquired Toxoplasmosis**

**Acute Induction Therapy (Followed by Chronic Suppressive Therapy):**

- **Pyrimethamine:** loading dose—2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, plus
- **Leucovorin (folinic acid)** 10 mg by mouth or IM with each dose of pyrimethamine, plus
- **Sulfadiazine** 50 mg/kg body weight by mouth twice daily

**Treatment Duration (Followed by Chronic Suppressive Therapy):**

- ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)

**Congenital Toxoplasmosis:**

- For infants born to mothers with symptomatic Toxoplasma infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother’s treatment during pregnancy.

**Acquired Toxoplasmosis:**

- Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing.
- **TMP-SMX**—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children.
- **Atovaquone** (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children.
- **Azithromycin** (for adults, 900–1,200 mg/day, corresponding to 20 mg/kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children.
- **Corticosteroids** (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and continued through the acute treatment; but should not be used prophylactically.

*Note: Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight.

**Key to Acronyms:**
cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole
### III. Table 3. Recommendations for prevention (prophylaxis) of *Pneumocystis jiroveci* pneumonia in adults and adolescents with HIV

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred regimen</th>
<th>Alternative regimens</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preventing First Episode of PCP</strong> <em>(Primary Prophylaxis)</em></td>
<td>TMP-SMX 1 DS tablet PO daily, or TMP-SMX 1 SS tablet daily</td>
<td>TMP-SMX 1 DS PO three times weekly, or Dapsone 100 mg PO daily or 50 mg PO BID, or Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or Atovaquone 1500 mg PO daily, or (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10mg) PO daily</td>
<td>CD4 count increased from &lt;200 cells/mm³ to ≥200 cells/mm³ for ≥3 months in response to ART Can consider when CD4 count is 100–200 cells/mm³ and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months</td>
</tr>
<tr>
<td><strong>Preventing Subsequent Episode of PCP</strong> <em>(Secondary Prophylaxis)</em></td>
<td>TMP-SMX 1 DS tablet PO daily, or TMP-SMX 1 SS tablet daily</td>
<td>TMP-SMX 1 DS tablet PO three times weekly, or Dapsone 100 mg PO daily, or Dapsone 50 mg PO twice daily, or Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly, or Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or Atovaquone 1500 mg PO daily with food, or (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily</td>
<td>CD4 count increased from 200 cells/mm³ for &gt;3 months as a result of ART, or Can consider if CD4 count is 100–200 cells/mm³ and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months For patients in whom PCP occurs at a CD4 count &gt;200 cells/mm³ while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 months to 6 months, although there are no data to support recommendations in this setting.</td>
</tr>
</tbody>
</table>

Note: If an episode of PCP occurs at a CD4 count >200 cells/mm³ while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART.

**Indications for Restarting Secondary Prophylaxis:**
- CD4 count <100 cells/mm³ regardless of HIV RNA
- CD4 count 100–200 cells/mm³ and HIV RNA above detection limit of the assay used

**Note:**
- Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis.
- Key to acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole.
IV. Table 4. Dose recommendations for the prevention and treatment of cystoisoporiasis in adults and adolescents with HIV

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred regimen</th>
<th>Alternative regimens</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cystoisoporiasis therapy infection</td>
<td>• TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or • TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days</td>
<td>For Patients with Sulfa Intolerance: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily, or • Ciprofloxacin 500 mg PO BID for 7 days</td>
<td>7- 10 days</td>
</tr>
<tr>
<td></td>
<td>• One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist • IV therapy for patients with potential or documented malabsorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Maintenance Therapy (Secondary Prophylaxis)</td>
<td>In Patients with CD4 Count &lt;200/mm³: • TMP-SMX (160 mg/800 mg) PO 3 times weekly</td>
<td>• TMP-SMX (160 mg/800 mg) PO daily, or • TMP-SMX (320 mg/1600 mg) PO 3 times weekly, or • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily, or • Ciprofloxacin 500 mg PO 3 times weekly as a second line alternative</td>
<td>Sustained increase in CD4 count &gt;200 cells/mm³ for &gt;6 months in response to ART and without evidence of active infection</td>
</tr>
</tbody>
</table>
V. Table 5. Dose recommendations for the prevention and treatment of cystoisoporiasis in HIV-Exposed and HIV-Infected Children³

<table>
<thead>
<tr>
<th>Indication</th>
<th>Preferred regimen</th>
<th>Alternative regimen</th>
<th>Treatment duration / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis</td>
<td>There are no U.S. recommendations for primary prophylaxis of isosporiasis.</td>
<td>Consider discontinuing secondary prophylaxis in a patient receiving cART after sustained improvement from severe immunosuppression (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for longer than 6 months. In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no similar data exist for children. Thus, the recommended dosing for secondary prophylaxis in children is 1 mg/kg per dose (maximum 25 mg) once daily. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.</td>
<td></td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>If Severe Immunosuppression: • Administer TMP-SMX 2.5 mg/kg body weight of TMP component twice daily by mouth 3 times per week</td>
<td>Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid, 10–25 mg by mouth once daily. Second-Line Alternative: • Ciprofloxacin, 10–20 mg/kg body weight given twice daily by mouth 3 times per week</td>
<td>If symptoms worsen or persist, the TMP-SMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.</td>
</tr>
<tr>
<td>Treatment</td>
<td>TMP-SMX 5 mg/kg body weight of TMP component given twice daily by mouth for 10 days</td>
<td>Pyrimethamine 1 mg/kg body weight plus folinic acid 10-25 mg by mouth once daily for 14 days Second-Line Alternatives: • Ciprofloxacin 10–20 mg/kg body weight/day twice daily by mouth for 7 days • Nitazoxanide for 3 consecutive days</td>
<td>If symptoms worsen or persist, the TMP-SMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; cART = combination antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole

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.
References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated criteria to policy format; Added initial and renewal length of authorization; Added toxoplasmosis prophylaxis, toxoplasmosis treatment, congenital toxoplasmosis, Pneumocystis jiroveci pneumonia prophylaxis, and cystoisoporiasis treatment intervention criteria for compound, generic, and brand product; Added brand Daraprim requirement; Added supporting evidence and dosing appendix.</td>
<td>06/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>02/2016</td>
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</tbody>
</table>
Recombinant Antihemophilic factor (Obizur®) – Acquired Hemophilia A
UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP020

Description
Obizur is an antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia. Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

Length of Authorization
- Initial: 6 months
- Renewal: 6 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obizur, antihemophilic factor (recombinant), porcine sequence</td>
<td>500 units</td>
<td>Treatment of bleeding episodes in adults with acquired hemophilia A: • Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 50-100 IU/dL every four to 12 hours • Major: Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 100-200 IU/dL (to treat acute bleed) every four to 12 hours, then 50-100 IU/dL (after acute bleed is controlled) every four to 12 hours</td>
<td>Treatment of bleeding episodes in adults with acquired hemophilia A: Up to the number of doses requested every 28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Obizur may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **acquired hemophilia A (acquired factor VIII deficiency)** when the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Diagnosis of acquired factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
      3. Used as treatment of bleeding episodes; **AND**
      4. Obizur is not being used for congenital hemophilia A or von Willebrand disease
II. Obizur is considered investigational when used for congenital hemophilia or von Willebrand disease, or any other condition.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Acquired inhibitors of coagulation are antibodies that either inhibit the activity or increase the clearance of a clotting factor. The most common autoantibodies that affect clotting factor activity and lead to a bleeding disorder are directed against, and interfere with, the activity of factor VIII. This condition is also called acquired hemophilia.

II. Obizur is a recombinant, B domain-deleted porcine (pig) factor VIII indicated for the treatment of patients with autoantibodies to factor VII (i.e. patients with an acquired factor VIII inhibitor). It is not approved for use in patients with congenital (i.e. inherited) hemophilia A.

III. The safety and efficacy of Obizur was established in a small prospective study in patients with an acquired factor VIII inhibitor and severe bleeding. Obizur controlled bleeding in 86% of patients.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of Obizur in any other condition.

References

1. Obizur® [Prescribing Information]. Lexington, MA: Baxalta; September 2017

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>August 2019</th>
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<tr>
<td>Date Effective</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy created for Obizur</td>
<td>08/2019</td>
</tr>
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Description
Regorafenib (Stivarga) is an orally administered kinase inhibitor acting on various membrane-bound and intracellular kinases.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

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

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

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iii. The member has previously progressed on or after an anti-VEGF therapy [e.g., bevacizumab (Avastin)]; **AND**

iv. The member has KRAS-mutated colorectal cancer; **OR**
   a. If KRAS wild-type, the member has been treated with an anti-EGFR therapy [e.g., cetuximab (Erbitux), panitumumab (Vectibix)]; **OR**

2. **Gastrointestinal Stromal Tumor; AND**
   i. The member has locally advanced (stage III), unresectable or metastatic (stage IV) disease; **AND**
   ii. The member has previously progressed on or after imatinib (Gleevec); **AND**
   The member has previously progressed on or after sunitinib (Sutent); **OR**

3. **Hepatocellular Carcinoma; AND**
   i. Provider attests the patient has Child-Pugh class A; **AND**
   ii. The member has previously progressed on or after sorafenib (Nexavar)

II. Regorafenib (Stivarga) is considered *investigational* when used for all other conditions, including but not limited to:
   A. Biliary cancer, cholangiocarcinoma
   B. Esophageal cancer (esophageal, gastroesophageal, gastric)
   C. Non-small cell lung cancer
   D. Renal cell carcinoma
   E. Soft tissue sarcoma
   F. Adenoid cystic carcinoma
   G. Urothelial carcinoma
   H. Ovarian cancer
   I. Osteosarcoma

**Renewal Evaluation**

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Regorafenib (Stivarga) will **not** be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**

IV. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

**Supporting Evidence**

I. Regorafenib (Stivarga) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

II. Due to the complex nature of treating any of the diagnoses regorafenib (Stivarga) is approved for, treatment should be prescribed by, or in consultation with, an oncologist.

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September 01, 2022
III. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study, the CORRECT trial, in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects, 505 in the regorafenib arm and 255 in the placebo arm, that had been previously treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, as well as bevacizumab (Avastin). All but one subject with KRAS wild-type disease received ANTI-EGFR therapy [cetuximab (Erbitux), panitumumab (Vectibix)]. Regorafenib (Stivarga) showed a statistically significant improvement in overall survival (OS) compared to placebo [6.4 months vs. 5 months; HR 0.77 (CI 0.64-0.94), p = 0.0102].

IV. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (GRID) in adults with unresectable, locally advanced or metastatic disease. A total of 199 patients, 133 in the regorafenib arm and 66 in the placebo arm, had been previously treated with imatinib (Gleevec) and sunitinib (Sutent). The medication showed a statistically significant improvement in progression-free survival (PFS) [PFS was 4.8 vs. 0.9 months; HR 0.27 (0.19-0.39), p<0.0001]; however, there was no statistical difference in OS. This may have been influenced by cross-over to active therapy after disease progression on placebo as patients were allowed to change to regorafenib after progression and 56 of the 66 patients moved to the treatment arm.

V. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in adults with hepatocellular carcinoma, Child-Pugh class A. All subjects (379 in the regorafenib arm and 194 in the placebo, 573 total) had documented disease progression on sorafenib (Nexavar), and those that had discontinued sorafenib (Nexavar) due to toxicity rather than disease progression were ineligible for the trial; thus, safety and efficacy with regorafenib (Stivarga) prior to progression on or after sorafenib (Nexavar) has not been established. Overall survival was the primary outcome and was statistically significant in favor of regorafenib (Stivarga) over placebo [10.6 vs. 7.8 months; HR 0.63 (0.5-0.79), p<0.0001].

VI. In the clinical trials, severe drug-induced liver injury with fatal outcomes did occur. In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo. These drug-induced injuries were typically high-grade elevation of bilirubin, AST, ALT, and ALP with risk of developing injury roughly two-fold in the regorafenib arms compared to placebo.

VII. As regorafenib was only studied in Child-Pugh class A (patients in the lower risk/best survival chances), safety of regorafenib in patients with Child-Pugh class B7 or beyond is unknown with the possibility of drug toxicity with worsening overall outcomes. Additionally, a clinical outreach to a key opinion leader (KOL) specializing in the treatment of liver cancer, agreed that use of regorafenib should be considered after failure of sorafenib, and only in patients with Child-Pugh class A liver status, as they have the best outcomes for a favorable prognosis while balancing the risk of treatment-induced hepatotoxicity. Additionally, the KOL expert noted that the best approach to the management of HCC patients with Child-Pugh class B7 or beyond may be via clinical trial enrollment or a liver transplant.

VIII. For all indications regorafenib (Stivarga) is dosed at 160 mg per day on days 1-21 of each 28-day cycle. Product availability is 40 mg tablets and for patients experiencing dose-dependent
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Intolerance (adverse reactions), the dose of regorafenib (Stivarga) should be reduced in 40mg increments, with the lowest recommended dose of 80mg/day.

Investigational or Not Medically Necessary Uses

I. Regorafenib (Stivarga) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
   A. Osteosarcoma
      i. First-line therapy for osteosarcoma is surgically removing the tissue/bone involved (either limb-sparing or limb-amputation) with radiation therapy followed by chemotherapy - based on the type and affected site of osteosarcoma (chondrosarcoma, Ewing sarcoma, Giant Cell Tumor of bone, etc.). Recommended systemic therapy options in this setting are: pembrolizumab (Keytruda), dasatinib (Sprycel), pazopanib (Votrient) or cisplatin/doxorubicin or MAP (high-dose methotrexate, cisplatin, and doxorubicin).
      ii. The NCCN panel updated guidelines to give regorafenib a category 1 recommendation for second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease), based on the following data of two phase 2 clinical trials (REGOBONE and SARC024) noting that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. However, at this time, regorafenib has not received FDA approval for the treatment of osteosarcoma.
      iii. In the REGOBONE study, the primary endpoint was the number of patients without disease progression at 8 weeks. Patients were randomly assigned 2:1 to regorafenib or placebo with 38 patient total in the end efficacy analysis. 17 of 26 patients in the regorafenib arm (65%) were non-progressive at 8 weeks compared with 0 patients in the placebo arm. Although a preliminary indicator of efficacy, these results were not statistically significant, neither the study powered to evaluate the difference between the treatment and placebo arms.
      iv. In the SARC024 (randomized, double-blind, phase 2 study), progression free survival (PFS) was the primary endpoint. SARC024 had 42 patients randomized 1:1 to regorafenib or placebo with allowance of crossover at time of disease progression. Median PFS was significantly improved with regorafenib versus placebo: 3.6 months (95% CI, 2.0 to 7.6 months) versus 1.7 months (95% CI, 1.2 to 1.8 months), respectively (hazard ratio, 0.42; 95% CI, 0.21 to 0.85; p 0.017). In the context of the crossover design, there was no statistically significant difference in overall survival. Additionally, based on consensus recommendations from the clinical experts, a progression-free survival (PFS) of ≥ 4months has been regarded as a clinically meaningful metric of positive outcomes in the setting of osteosarcoma, which this trial did not attain.
   B. Biliary cancer, cholangiocarcinoma
   C. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
   D. Non-small cell lung cancer
   E. Renal cell carcinoma
F. Soft tissue sarcoma  
G. Adenoid cystic carcinoma  
H. Urothelial carcinoma  
I. Ovarian cancer

References

7. Grothey A., Sobrero AF., Siena S., et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) or regorafenib plus best supportive care versus placebo in patients with metastatic colorectal cancer who have progressed after standard therapies.  

Related Policies

<table>
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<tr>
<th>Policy Name</th>
<th>Disease state</th>
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<tr>
<td>Avapritinib (Ayvakit)</td>
<td>Unresectable or metastatic gastrointestinal stromal tumor with PDGFRA exon 18 mutation</td>
</tr>
<tr>
<td>Cabozantinib (Cabometyx, Cometriq)</td>
<td>Progressive or metastatic hepatocellular carcinoma, in patients previously treated with sorafenib</td>
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<tr>
<td>Dasatinib (Sprycel)</td>
<td>Gastrointestinal Stromal Tumors (GIST)</td>
</tr>
<tr>
<td>Encorafenib (Braftovi), binimetinib (Mektovi)</td>
<td>Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy</td>
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<tr>
<td>Ripretinib (Qinlock)</td>
<td>Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors</td>
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<tr>
<td>Sunitinib (Sutent)</td>
<td>Gastrointestinal stromal tumor</td>
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September 01, 2022
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<table>
<thead>
<tr>
<th>Trifluridine/tipiracil (Lonsurf)</th>
<th>Colorectal cancer-metastatic, previously untreated</th>
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<tbody>
<tr>
<td>Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)</td>
<td>Unresectable hepatocellular carcinoma</td>
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**Policy Implementation/Update:**

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<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Added in Child-Pugh class A to hepatocellular cancer requirement based on KOL, NCCN, and clinical trial recommendations. Updated supporting evidence for the three FDA indications.</td>
<td>08/2022</td>
</tr>
<tr>
<td>Removed split fill</td>
<td>01/2022</td>
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<tr>
<td>Prior authorization transitioned to policy format. Addition of age edit, addition of monotherapy requirement. Renewal criteria transitioned to current formatting and language and increase from three to 12 month approval.</td>
<td>11/2019</td>
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<tr>
<td>Previous Reviews</td>
<td>01/2013; 02/2013; 04/2014; 09/2014;</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP228

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

Length of Authorization
- Initial: 12 months
- Renewal:
  i. Orgovyx: 12 months
  ii. Myfembree: 12 months, total (lifetime) fills not to exceed 24 28-day fills

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>relugolix (Orgovyx)</td>
<td>120 mg tablets</td>
<td>Prostate cancer</td>
<td>Initial: 30 tablets/28 days for one month</td>
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<td></td>
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<td>Maintenance: 30 tablets/30 days</td>
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<tr>
<td>relugolix/estradiol/norethindrone (Myfembree)</td>
<td>40 mg/1 mg/0.5 mg tablets</td>
<td>Heavy menstrual bleeding associated with uterine fibroids (leiomyoma)</td>
<td>28 tablets/28 days</td>
</tr>
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</table>

Initial Evaluation

I. Relugolix (Orgovyx) or relugolix/estradiol/norethindrone (Myfembree) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. For relugolix (Orgovyx):
      1. A diagnosis of prostate cancer; AND
         i. Medication is prescribed by, or in consultation with, an oncologist or urologist; AND
         ii. Provider attestation the member is castration sensitive; AND
         iii. Prostate cancer is advanced or metastatic (Stage III or IV); AND
         iv. Treatment with a GnRH agonist (e.g., leuprolide [Lupron]), has been ineffective, not tolerated, or all GnRH agonists are contraindicated; OR
            a. The member has a history of a major adverse cardiovascular event (MACE) (e.g., myocardial infarction, stroke); AND
            v. Degarelix (Firmagon) has been ineffective, not tolerated, or is contraindicated; AND
vi. Relugolix (Orgovyx) is medically necessary for the treatment of prostate cancer over GnRH agonists and degarelix (Firmagon). (Note – preference for oral administration or other convenience does not meet medical necessity); OR

C. For relugolix/estradiol/norethindrone (Myfembree):
   1. A diagnosis of heavy menstrual bleeding associated with uterine fibroids (leiomyoma); AND
      i. Medication is prescribed by, or in consultation with, an obstetrician/gynecologist; AND
      ii. Member does not have a history of osteoporosis (defined as T-score less than or equal to -2.5 or Z-score less than -1.5 at the lumbar spine, femoral neck or total hip); AND
      iii. At least one hormonal contraceptive treatment (oral, IUD, implant, etc.) has been ineffective, not tolerated, or ALL are contraindicated; AND
      iv. Treatment with tranexamic acid has been ineffective, not tolerated, or is contraindicated; AND
      v. Provider attestation that the member has not previously been treated with elagolix/estradiol/norethindrone (Oriahnn).

II. Relugolix is considered investigational when used for all other conditions, including but not limited to:
   A. Endometriosis, treatment or symptom management
   B. Castration-resistant prostate cancer

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND

III. Relugolix (Orgovyx):
   A. Documentation of disease response to treatment (e.g., stabilization of disease or decrease in tumor size or tumor spread, reduction in serum testosterone or PSA); OR
   B. Provider attestation that continuation of therapy is necessary if the member has had disease progression; OR

IV. Relugolix/estradiol/norethindrone (Myfembree):
   A. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improvement in quality of life, etc.); AND
   B. Provider attestation the member has not previously received treatment with elagolix/estradiol/norethindrone (Oriahnn); AND
   C. The member has not received treatment for more than 24 months

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September 01, 2022
Supporting Evidence

I. Relugolix (Orgovyx) is a gonadotropin-releasing hormone (GnRH) receptor antagonist, FDA-approved for the treatment advanced prostate cancer. A 360 mg loading dose (three tablets) is administered on day one, then a maintenance dose of 120 mg (one tablet) is taken once daily. It is one of several androgen deprivation therapies (ADT) available. Other options include GnRH agonists such as leuprolide (Lupron), goserelin (Zoladex), triptorelin (Telstar/Triptodur), histrelin (Supprelin LA, Vantas), and GnRH agonist [degarelix (Firmagon)], all of which are injectable medications. Additionally, surgical orchiectomy is an option when prompt castration is required. Reducing serum testosterone to castrate levels is warranted for the treatment of prostate cancer, and all of these methods are highly effective. Androgen deprivation therapy is a hallmark of treatment, and is generally continued, if tolerated, even if there is progressive disease and/or if other prostate cancer medications are started. Given the specialization of the condition and treatment options, therapy should be prescribed by, or in consultation with, an oncologist.

II. The GnRH agonists are highly utilized for the treatment of advanced or metastatic prostate cancer. They are known to cause a testosterone surge upon initiation, with a subsequent decrease in serum testosterone three-to-four weeks after starting treatment. For patients at risk for these symptoms, an antiandrogen therapy (e.g., flutamide, nilutamide, bicalutamide) may be administered concurrently for the first few weeks of GnRH agonist treatment. Some agents are available in every three-month injections and are generally well tolerated.

III. The GnRH antagonists, degarelix (Firmagon), and now relugolix (Orgovyx), are successful at mitigating the testosterone surge and may rapidly reduce testosterone; although, the rapidity of testosterone suppression with GnRH antagonists has not been linked to superior clinical benefit over the GnRH agonists in the general population likely to utilize these therapies.

IV. Relugolix (Orgovyx) was evaluated in one Phase 3, randomized, open-label, non-inferiority (NI) trial vs. leuprolide (Lupron) over 48 weeks in patients with advanced or metastatic disease. Up to 13% of patients had previous ADT, 30% had previous radiotherapy, and 14% had a history of major adverse cardiovascular event (MACE). There was a washout period of three months for those previously treated with degarelix (Firmagon) and one year for those on GnRH agonist therapy. Those with a MACE in the six months before the trial were excluded. All patients included in the trial were adults, which is the expected population to be diagnosed with prostate cancer. At this time the safety and efficacy of relugolix (Orgovyx) in pediatric patients remains unknown; however, it would be very rare for a pediatric patient to develop prostate cancer.

V. The primary outcome was cumulative sustained castration rate of less than 50 ng/dL from day 29 through 48 weeks. Results were 96.7% of patients for relugolix (Orgovyx) and 88.8% for leuprolide (Lupron), with a difference of 7.9% (CI 4.1-11.8). Additionally, a notable secondary outcome was castration relapse free survival (CRFS) at 48 weeks. This was 74% for relugolix (Orgovyx) and 75% for leuprolide (Lupron) (HR 1.03, CI 0.68-1.57, p=0.84). Both of these outcomes showed NI of relugolix (Orgovyx) to leuprolide (Lupron). Statistically, relugolix (Orgovyx) was superior to leuprolide (Lupron) in the primary outcome; however, both therapies showed a very high rate of sustained castration. At this time definitive data are lacking to indicate clinical superiority of either product in regard to medication efficacy.

VI. There were several other secondary outcomes measured: probability of testosterone suppression to less than 50 ng/dL on day four and day 15, prostate specific antigen (PSA)...
response on day 15 and day 29, probability of profound testosterone suppression (less than 20 ng/dL) on day 15. These were all superior for relugolix (Orgovyx) over leuprolide (Lupron). This is expected given the mechanistic differences of the therapies. Given the known initial testosterone surge with GnRH agonists, castrate levels would be expected three-to-four weeks after medication initiation. The results confirm the rapidity of testosterone suppression for relugolix (Orgovyx), as expected for a GnRH antagonist.

VII. Rate of overall adverse events (AE) was consistent across both groups. Common AE (greater than 10%) that occurred in both groups included laboratory abnormalities, increase glucose levels, increase triglycerides, musculoskeletal pain, increased hemoglobin, ALT/AST increases, constipation, and diarrhea.

VIII. Serious AE occurred in 9.8% of the relugolix (Orgovyx) group, and 15.3% of the leuprolide (Lupron) group. For relugolix (Orgovyx) sAE: myocardial infarction (0.8%), AKI (0.6%), hemorrhage (0.6%), and UTI (0.5%).

IX. The MACE rate was 2.9% for relugolix (Orgovyx) and 6.2% for leuprolide (Lupron), overall. This was further pronounced in the subgroup of patients that had a previous MACE. Rates were 3.6% and 17.8%, respectively. In the group without a previous MACE, rates were 2.8% and 4.2%, respectively. From the data, it is predicted that GnRH antagonists may have a favorable safety profile in those with history of a MACE, such as myocardial infarction and stroke. Options include degarelix (Firmagon) as well as relugolix (Orgovyx), and current data are lacking to indicate clinical favorability between these two agents.

X. Relugolix/estradiol/norethindrone (Myfembree) was evaluated in the setting of heavy menstrual bleeding associated with uterine fibroids (leiomyoma). Fibroids are commonly experienced by women that are premenopausal, and are associated with heavy menstrual bleeding, pain, and anemia. Management strategies for uterine fibroids include hysteroscopic fibroid resection, estrogen-progestin contraceptives, progestin-releasing intrauterine devices, progestin-only contraceptives, tranexamic acid, GnRH antagonists (e.g., Lupron), GnRH agonists (e.g., Oriahnn), uterine artery embolization, hysterectomy, and endometrial ablation.

XI. Treatment choice is dependent on fibroid size, patient age, fertility preference, symptoms, and other patient related factors. Hysterectomy is the only definitive cure, but myomectomy may be preferred for women with submucosal fibroids wishing to preserve the uterus. Medication therapy may be preferred for management to either prolong time to surgery or as preoperative treatment in preparation for surgery. Given the complex treatment choices and risks associated with each, therapy should be directed by or in consultation with a specialist.

XII. The most common medication therapy utilized for the management of uterine fibroids includes estrogen-progestin contraceptives (e.g., pills, rings, patches) and progestin IUDs. These interventions do not change affect the pathology of the fibroids, but they are accepted as a standard management strategy to reduce the heavy menstrual bleeding. Tranexamic acid is a nonhormonal treatment that may be used during menstruation to reduce heavy bleeding.

XIII. As the safety profiles often limit their use, GnRH agonists and antagonists are second-line medications. GnRH agonists (e.g., Lupron) are often used for a few months preoperatively to reduce fibroid size, or to bridge a patient into menopause. For GnRH antagonists, relugolix/estradiol/norethindrone (Myfembree) will join elagolix/estradiol/norethindrone (Oriahnn) for the treatment of this indication. Acute tolerability is generally more favorable, but long-term safety and efficacy data are limited. Additionally, there is a known decrease in bone
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mineral density (BMD) which limits treatment duration. Furthermore, the safety of utilizing GnRH antagonists subsequently at their full FDA-approved duration is unknown, and would be expected to exacerbate the decrease in BMD.

XIV. Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two Phase 3, double-blind, randomized, placebo-controlled trials over 24 weeks. Therapy was evaluated in premenopausal women with heavy menstrual bleeding and diagnosis of uterine fibroids, confirmed via ultrasonography. Patients with osteoporosis or osteopenia were excluded.

XV. Primary outcome: percentage of participants with treatment response (blood loss volume < 80 mL and ≥ 50% reduction in volume). Secondary outcomes: proportion of patients reaching amenorrhea, change in blood loss volume, pain, distress from bleeding and pelvic discomfort, and participants that had a change in hemoglobin of 2 g/dL or more in those that had anemia at baseline. These outcomes were statistically and clinically significant over placebo. In clinical trials, relugolix/estradiol/norethindrone (Myfembree) did not reduce uterine fibroid volume.

XVI. Relugolix was also evaluated as monotherapy in a randomized, blinded, NI trial vs. leuprorelin (Lupron). Relugolix showed to be NI to leuprorelin (Lupron) in the following outcomes: blood loss, amenorrhea, uterine volume, fibroid volume, hemoglobin improvement, pain, and quality of life. Estrogenic AE and decrease in BMD were notable; thus, the manufacturer is pursuing combination therapy with estradiol and norethindrone to mitigate these concerns. A limitation of the trial is the majority of patients received leuprorelin (Lupron) 1.88 mg, rather than the standard U.S. dose of 3.75 mg. Comparative safety and efficacy data to the 3.75 mg dose of leuprorelin (Lupron) is currently unknown.

XVII. Rate of overall AEs was consistent for placebo and active therapy. No deaths occurred in the trials and serious AEs were rare. There were a few cases of ankle fracture in those that received relugolix/estradiol/norethindrone (Myfembree). At week 24 the BMD at lumbar spine and total hip were similar between groups. AE leading to treatment discontinuation occurred in 4-11% of patients. Common AE included the following: hot flash (6-11% vs. 4-8% for placebo) and hypertension (5% vs. 0% for placebo). Other AE that occurred in ≥ 5% of patients included headache, arthralgia, cough, nausea, URI, fatigue, and anemia. Long term safety is currently unknown but will be better understood with results from long-term safety extension trials. The FDA has indicated that use of Myfembree should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

**Investigational or Not Medically Necessary Uses**

1. Relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Endometriosis, treatment or symptom management
   B. Castration-resistant prostate cancer

**References**


**Policy Implementation/Update:**

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Washington State Rx Services is administered by moda HEALTH

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September 01, 2022
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP117

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

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

Quantity limits

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<td>Infantile Spasms (West Syndrome)</td>
<td>80 units/mL vial (400 units/5mL)</td>
<td>Monthly quantity in mL to allow for: 150 u/m² daily for two weeks plus a two-week taper as follows: three days’ worth of 30 u/m², three days’ worth of 15 u/m², six days’ worth of 10 u/m²</td>
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Initial Evaluation

I. Repository corticotropin (Acthar, Cortrophin) gel may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neurologist; AND
   B. A diagnosis of one of Infantile Spasms (West Syndrome); AND
      1. Member is under two years of age; AND
      2. Medication to be used as monotherapy; AND
      3. Documentation of recent body surface area; OR
         i. Documentation of member’s height and weight (needed for dose calculation).

II. Repository corticotropin (Acthar, Cortrophin) gel is considered not medically necessary when criteria above are not met and/or when used for the following:
   A. Multiple sclerosis
   B. Rheumatoid arthritis
   C. Psoriatic arthritis
   D. Ankylosing spondylitis
   E. Dermatomyositis/polymyositis
F. Optic neuritis (40 units daily, also included in investigational section for other doses, see below)
G. For use in nephrotic syndrome over corticosteroid therapy (also included in investigational section, see below)

III. Repository corticotropin (Acthar, Cortrophin) is considered investigational when used for all other conditions, including but not limited to:
A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome)
B. Ophthalmic conditions and diseases: keratoconjunctivitis sicca, Sjogren’s syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis, optic neuritis, etc.
C. Nephrotic syndrome (NS) and NS due to focal segmental glomerulosclerosis (FSGS) or immunoglobulin A nephropathy (IgAN)
D. Juvenile rheumatoid arthritis
E. Lupus erythematosus
F. Dermatologic conditions: erythema multiforme, Steven’s Johnson syndrome
G. Serum sickness
H. Sarcoidosis

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

Supporting Evidence
I. Infantile spasms (West Syndrome): Repository corticotropin (Acthar, Cortrophin) gel is an ACTH analogue that acts similarly to corticosteroids and was FDA-approved for infantile spasms in 2010. Data from several randomized controlled trials are available to support safety and efficacy. One clinical trial showed superiority over prednisone in the proportion of patient responders to therapy. Other studies directly comparing therapy to corticosteroids did not determine
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statistical superiority of repository corticotropin (Acthar) gel. Although data for superiority of repository corticotropin (Acthar) gel over corticosteroids are conflicting, there is insufficient evidence to support that corticosteroids could be more effective than repository corticotropin (Acthar) gel. Guidelines recommend repository corticotropin (Acthar) as the mainstay therapy.

- Infantile spasms are characterized as epileptic spasms that appear in infancy and early childhood. The majority of patients will present before seven months of age, and the condition is associated with electroencephalographic pattern of hypsarrhythmia. This medication has been evaluated and is only FDA-approved for patients under two years of age. In patients older than two years, alternative cost-effective treatment options should be considered.

- In clinical practice, repository corticotropin (Acthar) gel has been utilized at a variety of doses. The FDA-approved dose (which has also been evaluated in several clinical trials) is as follows: 150 units/m² daily (divided between twice daily) for two weeks plus a two-week taper: three days each of 30 units/m², 15 units/m², 10 units/m², followed by 10 units/m² every other day for six days. The last six days of therapy equates to total of three additional days of 10 units/m² (equating to six full days of the 10 units/m² dose). Several studies have evaluated differing dosing regimens, including lower doses. In the event under dosing is prescribed relative to the FDA-approved dose, this regimen should be allowed given some evidence to indicate that lower doses may be as effective as that FDA-approved. Repository corticotropin (Acthar) gel has been evaluated in clinical trials using 150 units/m² for three weeks then a taper for three more weeks; however, this higher dose group did not show superior efficacy to lower doses. Similar rates of response and relapse occurred; thus, at this time there is no evidence to support need for a longer than two-week duration of 150 units/m² per day.

- Duration of initial therapy with treatment and taper is four weeks. Response is expected in the first few weeks. There is lack of evidence to support extended use of therapy; however, a second course of therapy may be appropriate for patients that relapse and require retreatment. Lack of response (i.e., number/severity of spasms) on first treatment course signals an alternative regimen should be utilized for retreatment; thus, response to the initial therapy course is required. Long-term safety is similar to corticosteroids: cardiac, ocular, mood, sleep, skin concerns, etc.

- Repository corticotropin (Cortrophin) gel is not FDA-approved for the indication of infantile spasms; however, is not expected to have any clinical differences. This is a more cost-effective treatment option, and when other criteria are met for the indication of infantile spasms, Cortrophin use is covered under the specifications listed above (e.g., QLL, etc.). ANI Pharmaceuticals received FDA-approval of Purified Cortrophin gel in November 2021, in efforts to support broader and more cost-effective access to corticotropin products.

II. Repository corticotropin (Acthar) gel was FDA-approved in 1952 and Cortrophin gel was approved in 1954 for the treatment of inflammatory conditions prior to current FDA standards, and the indications were grandfathered into the labels; however, corticotropin products have not demonstrated evidence for safety and efficacy, or medical necessity over corticosteroids, for the majority of the labeled indications. Furthermore, the cost has increased significantly over the past few decades: $36 per vial in 2001; in 2022, $49,750 per vial for Acthar and $38,200 for...
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.

**Investigational or Not Medically Necessary Uses**

*Disclaimer: In the event an approval is granted for corticotropin for any condition outside of infantile spasms (West Syndrome), Acthar will only be allowed after a sufficient trial and failure of Cortrophin, supported with documentation and rationale.*

I. Repository corticotropin (Acthar, Cortrophin) (ACTH) gel is considered not medically necessary for the following conditions:

A. Multiple sclerosis: At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroids, given lack of quality trials and trials with consistent results showing superiority; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary for MS and is not covered. Furthermore, choice of or success of therapy in acute MS exacerbation has not been correlated with improved or superior long-term outcomes, further reducing the necessity of ACTH gel for this condition.

B. Rheumatoid arthritis, psoriatic arthritis, dermatomyositis/polymyositis, ankylosing spondylitis: ACTH gel has been evaluated in Phase 4, randomized, placebo-controlled withdrawal studies for these conditions in addition to several lesser quality trials. In some trials, therapy was superior to placebo for disease response; however, this medication has not been directly compared to NSAIDS, the majority of systemic corticosteroids, conventional synthetic DMARDs, specialty DMARDS, and biologic therapies. Numerous other medications have strong evidence for safety and efficacy, all of which are more cost-effective. At this time, it is unproven if ACTH gel is more likely to produce similar therapeutics results or is superior to other therapies; however, ACTH gel is more costly than other therapies that could be utilized. Furthermore, ACTH gel is not recognized as an appropriate therapy per guidelines or standard practice; thus, is considered not medically necessary and is not covered.

C. Optic neuritis (also considered experimental and investigational, see below): ACTH gel was evaluated in one RCT vs. placebo, where 40 units daily for 30 days did not provide significant changes over placebo in visual acuity and visual field scores. Given that it is not known if therapy improves therapeutic outcomes at this dose, ACTH gel is considered not medically necessary and is not covered.

D. Nephrotic syndrome: superiority of ACTH gel over corticosteroids and other treatment options for this condition has not been demonstrated; certain trials have shown lack of benefit over placebo therapy and one clinical trial showed noninferiority to methylprednisolone. At this time, it is unproven if ACTH gel is more likely to provide...
similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary and is not covered.

II. Repository corticotropin (Acthar, Cortrophin) gel has not been sufficiently studied for safety and efficacy, and are considered experimental and investigational, for the following conditions or settings below:

A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome): ACTH gel has only been evaluated as monotherapy for the treatment of infantile spasms. There is unknown safety and efficacy when utilized for other anti-epileptic medications. When combination therapy is indicated vigabatrin plus corticosteroids may be considered as available evidence for efficacy and safety.

B. Systemic lupus erythematosus (SLE): Evaluated in a single-arm, open-label, four-week trial in 10 patients. This trial does not provide any certainty in the benefit of ACTH gel for SLE given the significant trial biases: subjective outcomes in an open-label trial, no comparator to be able to determine extent of benefit over placebo (if any), few patients evaluated, and concomitant medications which may have impacted/influenced the changes.

C. Optic neuritis (ON) (higher doses): Evaluated in a single-arm, open-label, 2-week trial at a starting dose of 80 units daily in 24 patients with ON. This trial does not provide any certainty in the benefit of therapy for ON given the significant biases in the trial: subjective outcomes in an open-label trial, few patients evaluated, short trial duration, and patients were on background therapies at the start of the trial, with no washout period. Results/conclusions seen in this assessment may not be attributable to ACTH gel.

D. Sarcoidosis: Evaluated for sarcoidosis in one retrospective medical record review, on provider assessment of “patients’ health status”. The trial showed that use of concomitant medications such as glucocorticoids decreased with use of ACTH gel. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases: retrospective trial design, subjective and invalidated outcomes in a nonblinded trial, most patients were on background therapies. Results/conclusions seen in this assessment may not be attributable to ACTH gel.

E. Nephrotic Syndrome (NS), including but not limited to those with FSGS: Evaluated in retrospective case series; a prospective, open-label, single arm trial, a randomized noninferiority trial vs. methylprednisolone with cytotoxic therapies; a randomized, placebo-controlled trial; a dose comparison trial; and one Cochrane systematic review evaluated in one retrospective case series in 44 patients (15 patients had FSGS). Data are heavily conflicting, none of which strongly point to medication benefit. For example, one of the randomized controlled trials showed no substantial differences compared to no therapy and the trial was ended early for no benefit. In the noninferiority trial, similar responses were seen to methylprednisolone. The Cochrane review determined lack of sufficient data to draw conclusions of efficacy and safety. The collection of data does not provide certainty of benefit of therapy for NS, is considered experimental and investigational, and is not covered by the health plan. At this time, it is also unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could
be utilized. Thus, ACTH gel is also not medically necessary over corticosteroids and is not covered.

i. NS due to immunoglobulin A nephropathy (IgAN): ACTH gel was evaluated in a single-arm, open-label pilot study in 19 patients. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to small number of patients in the trial, lack of comparator arm, and the majority of outcomes were unchanged at follow-up.

F. Ophthalmic conditions and diseases, including but not limited to: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis:

i. Keratitis/dry eye disease: ACTH gel was evaluated in a single-arm, open-label study in 35 patients with keratitis. The trial observed a 12-point change in IDEEL score for 17 patients (50%) with severe keratitis. ACTH gel was also evaluated in a single-arm, open-label pilot study in dry eye disease in 15 patients. The study evaluated the SANDE questionnaire for patient reported improvement; however, these trials do not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies may not have been reported so any results or conclusions may not be attributable to ACTH gel. Furthermore, the SANDE score is not a validated measurement tool for clinically meaningful change in dry eye comfort or symptom improvement.

1. Alternative therapies and management strategies include, but may not be limited to: avoidance of offending medications, environmental management, moisture conserving eyewear, ocular lubricants, artificial tears and preservative-free artificial tears (gels, ointments, drops), ophthalmic cyclosporine (generic, Restasis, Cequa), ophthalmic lifitegrast (Xidra), nasal varenicline (Tyrvaya), punctal plugs or occlusion, topical steroids, therapeutic contact lenses, autologous serum tear preparations.

ii. Uveitis: ACTH gel has been evaluated for uveitis in one retrospective trial evaluating medical record data of provider assessment on patients' health status for 91 patients. Trial conclusions were that provider reported improved patient status; however, this trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies were utilized by 100% of patients (including steroid eye drops, oral steroids, intraocular steroids, and non-steroid eye drops) so any results or conclusions may not be attributable to ACTH gel.

III. Juvenile rheumatoid arthritis

IV. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome

V. Serum sickness

VI. Sarcoidosis
Appendix

I. Methods to calculate body surface area include, but are not limited to the Mosteller method: BSA (m²) = Square root ((Ht (cm) x Wt (kg))/3600)

References

9. Multiple Sclerosis Association of America. Treating Multiple Sclerosis Relapse. October 2017. Available at: https://mymsaa.org/ms-information/treatments/relapses/

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September 01, 2022


Related Policies

Currently there are no related policies.

Policy Implementation/Update:

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<td>Policy criteria updated for infantile spasms indication: removal of congenital infection rule out, addition of body surface (or height and weight) requirement for dose calculation. Change of renewal criteria to check that patients still meet initial requirements and that member has had a response to therapy that would predict response with a retreatment. Criteria updated to allow for maximum of two courses per lifetime. Supporting evidence updated for infantile spasms, not medically necessary and experimental and investigational designations and information added for supporting evidence. Addition of Cortrophin to policy. Formatting updates.</td>
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September 01, 2022
Policy Type: PA  
Pharmacy Coverage Policy: UMP056

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

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

Quantity limits

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<td>Treatment of irritable bowel syndrome with diarrhea (IBS-D).</td>
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<td>Hepatic encephalopathy recurrence.</td>
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Initial Evaluation
I. Rifaximin (Xifaxan) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      i. Irritable Bowel Syndrome with Diarrhea (IBS-D); AND
         a. Member is 18 year of age or older; AND
         b. Rifaxamin (Xifaxan) is prescribed by or in consultation with a gastroenterologist; AND
         c. Treatment with at least three therapies from different groups have been tried and failed, not tolerated or all are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining classes will be required):
            a. Group 1: antidiarrheal (e.g., loperamide, bismuth subsalicylate, diphenoxylate/atropine, paregoric)
            b. Group 2: bile acid sequestrant (e.g., cholestyramine, colestipol)
            c. Group 3: antispasmodic (e.g., dicyclomine, hyoscyamine)
d. Group 4: Tricyclic serotonergic agent: (e.g., amitriptyline, nortriptyline, imipramine, desipramine)

OR

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

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

II. Rifaximin (Xifaxan) is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Small Intestinal Bacterial Overgrowth (SIBO)

**Renewal Evaluation**

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

II. **Hepatic encephalopathy; AND**
   A. Clinical documentation indicating disease stability or improvement.

**Supporting Evidence**

I. Rifaximin (Xifaxan) is indicated for adults and pediatric patients 12 years of age and older with travelers’ diarrhea, and adults older than 18 years of age with hepatic encephalopathy or IBS-D. Infectious Diseases Society of America clinical practice guidelines recommend treatment with fluoroquinolones or azithromycin as first line treatment of travelers’ diarrhea.

II. The FDA approved dose is 200 mg three times daily for three days for traveler’s diarrhea.

III. The American Association for the Study of Liver Diseases and European Association for the Study of the Liver clinical practice guidelines suggest initial therapy with lactulose for the treatment of hepatic encephalopathy. Rifaximin (Xifaxan) is an effective add-on therapy to lactulose for prevention of recurrence.

IV. Treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants. The American College of Gastroenterology gave moderate or weak recommendations for all IBS-D therapies due to poor quality of evidence and applicability to patient groups. Due to insufficient comparative evidence for efficacy, other treatment options provide a better value over rifaximin (Xifaxan). Of the antidepressants, tricyclic agents have...
shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

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

Investigational or Not Medically Necessary Uses

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

References

**Policy Implementation/Update:**

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<td>Last Reviewed</td>
<td>08/2015; 04/2019, 07/2019</td>
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**Action and Summary of Changes**

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

Pharmacy Coverage Policy: UMP214

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

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

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<td>riluzole (Exervan)</td>
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*Generic riluzole is a formulary agent and does not require prior authorization

Initial Evaluation

I. Riluzole (Rilutek, Tiglutik, Exervan) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Amyotrophic lateral sclerosis (ALS)**; **AND**
   D. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated.

II. Riluzole (Rilutek, Tiglutik, Exervan) are considered **investigational** when used for all other conditions, including but not limited to:
   A. Treatment-resistant depression
   B. Chorea in Huntington’s disease

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise.; **AND**

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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.
III. Documentation of clinical benefit, including stabilization of disease and absence of unacceptable toxicity from the drug [e.g. hepatic injury, severe neutropenia, interstitial lung disease]; **AND**

IV. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated

**Supporting Evidence**

I. According to the American Academy of Neurology (AAN) two randomized controlled clinical trials and one cross-sectional study, show that multidisciplinary clinics specializing in ALS care are likely effective in several ways, which include improved quality of life and lengthened survival. The AAN guidelines recommend that specialized multidisciplinary clinical referral should be considered for patients with ALS to optimize health care delivery and prolong survival and may be linked to enhanced quality of life.

II. The safety and efficacy of riluzole (Rilutek®) in pediatric patients with amyotrophic lateral sclerosis (ALS) has not been established.

III. According to the American Academy of Neurology (AAN) practice parameter for the care of patients with ALS, riluzole is safe and effective for slowing disease progression to a modest degree in ALS. They therefore recommend that riluzole should be offered to slow disease progression in patients with ALS.

**Investigational or Not Medically Necessary Uses**

I. In a randomized, double-blind, placebo-controlled sequential trial that evaluated the efficacy and safety of adjunctive riluzole for treatment-resistant major depressive disorder (MDD), 104 participants were randomized in a 2:3:3 ratio to receive riluzole/riluzole, placebo/placebo and placebo/riluzole. The trial had two phases of 4 weeks each, and the primary endpoint was change in depression severity as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), which did not show a statistically significant difference between riluzole and placebo.

II. Chorea is a hallmark of Huntington Disease (HD), along with cognitive decline and psychiatric impairment. The AAN guidelines for pharmacologic treatment of HD, notes two randomized controlled trials evaluating riluzole for chorea for HD using different doses (100 mg or 200 mg) and durations (8 weeks and 3 years). The first study (n=63) showed a statistically significant reduction in unified huntington’s disease rating scale (UHDRS) in patients who received riluzole 200 mg/day (-2.2 ± 3.3, p 0.01); however, statistical significance was observed in those who received riluzole 100 mg/day [-0.2 ± 2.9; vs placebo (± 0.7 ± 3.4)]. In the second study (n=537), no statistically significant difference in UHDRS chorea scores at 3 years was observed between participants who received riluzole 50 mg twice daily and placebo. Although the guidelines recommend riluzole 200 mg/day with level B of evidence for HD chorea, there is modest evidence on the efficacy and safety of riluzole for chorea in HD.

**References**


Policy Implementation/Update:

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<td>09/2021</td>
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<td>Criteria changed to policy format, added age requirement, specialist referral/prescription, step through generic riluzole tablet and renewal evaluation.</td>
<td>12/2020</td>
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Policy Type: PA

Pharmacy Coverage Policy: UMP207

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

Length of Authorization
   I. Initial: Three months
      • Renewal: 12 months

Quantity Limits

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<td>ripretinib (Qinlock)</td>
<td>50 mg tablets</td>
<td>Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors, including imatinib</td>
<td>90 tablets/30 days</td>
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Initial Evaluation
I. Ripretinib (Qinlock) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with any other oncology therapy); **AND**
   D. A diagnosis of **Gastrointestinal Stromal Tumor (GIST)** when the following are met:
      1. Member has advanced (Stage III), unresectable or metastatic (Stage IV) disease; **AND**
      2. Member has previously progressed on, or after, **ALL** of the following:
         a. imatinib (e.g., Gleevec)
         b. sunitinib (Sutent)
         c. regorafenib (Stivarga)

II. Ripretinib (Qinlock) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Third-line or prior treatment of gastrointestinal stromal tumor
   B. Advanced Systemic Mastocytosis or other hematologic malignancies
   C. Soft Tissue Sarcoma, outside of gastrointestinal stromal tumor
   D. Malignant Gliomas
   E. Melanoma
   F. Germ Cell, Penile Cancer

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.

September 01, 2022
G. Non-Small Cell Lung Carcinoma (NSCLC)
H. Other Advanced Solid Tumor Cancers/Malignancies

Renewal Evaluation

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

Supporting Evidence

I. Ripretinib (Qinlock) was evaluated in INVICTUS - a randomized (2:1), double-blind, placebo-controlled study in adults with advanced gastrointestinal stromal tumors. The trial included 129 subjects who had previously progressed on or after imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications. Mutation status was collected but was not utilized as part of the inclusion criteria for this trial. Ripretinib (Qinlock) was evaluated as monotherapy, and use of ripretinib (Qinlock) in addition to other oncologic therapies has not been evaluated for safety and/or efficacy.

II. The primary efficacy endpoint was progression-free survival (PFS) and notable secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QOL). Ripretinib (Qinlock) showed statistically significant results in PFS compared to placebo [6.3 months vs. 1.0 months; HR 0.15; 95% CI 0.09-0.25; p<0.01]; however, there was not a statistically significant difference in ORR. Due to a hierarchal testing procedure of endpoints, overall survival and quality of life could not be formally tested for statistical significance given the insignificance of the ORR result.

III. The safety profile of ripretinib (Qinlock) is similar to that of other TKIs. The most common treatment-related treatment emergent adverse events (occurring in 20% or more of patients in the ripretinib group) during the INVICTUS trial included alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia (also known as hand-foot syndrome), and diarrhea. There are no contraindications to ripretinib (Qinlock); however, warnings and precautions include: palmar-plantar erythrodysesthesia syndrome, new primary cutaneous malignancies, hypertension, cardiac dysfunction, risk of impaired wound healing, and embryo-fetal toxicity. Ripretinib (Qinlock) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients. FDA-approval has only been granted for adult patients.

IV. Gastrointestinal Stromal Tumor (GIST) is a rare subtype of soft tissue sarcoma, thus a definitive diagnosis from a specialty provider is warranted.
V. NCCN Guidelines recommend ripretinib (Qinlock) as fourth-line therapy for the treatment of unresectable or metastatic GIST for those who have progressed after imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga) with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

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

References


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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP208

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<td>risdiplam (Evrysdi)</td>
<td>Spinal Muscular Atrophy</td>
<td>60 mg/80 mL (0.75 mg/mL) solution</td>
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Initial Evaluation

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

ii. **Members two years of age or older:**
   a. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), **OR** Six-Minute Walk Test (6MWT).

II. Risdiplam (Evrysdi) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Use in members with Type IV SMA
   B. Used in combination with nusinersen (Spinraza)

**Renewal Evaluation**

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

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

III. Member has responded to therapy, defined as stability or improvement in net motor function/milestones, compared to pretreatment baseline as exemplified by at least ONE of the following:
   A. **Members less than two years of age:**
      1. Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurologic Exam (HINE), **OR** Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22; **OR**
   B. **Members two years of age or older:**
      1. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), **OR** Six-Minute Walk Test (6MWT); **OR**
   C. Provider attests that member has had a slowed rate of decline in the aforementioned measures compared to pretreatment rate.

**Supporting Evidence**

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

III. Risdiplam (Evrysdi) is being evaluated in two ongoing Phase 2/3 trials (FIREFISH, SUNFISH) and an ongoing, phase 2 trial (RAINBOWFISH). FIREFISH is evaluating patients with infantile-onset Type I SMA and SUNFISH is evaluating patients with later-onset Type II and non-ambulatory Type III. RAINBOWFISH is enrolling pre-symptomatic infants two months of age or younger with SMA. All three studies require a confirmed diagnosis of 5q-autosomal recessive SMA prior to enrollment. Patients requiring invasive ventilation or tracheostomy are excluded from all three clinical trials (FIREFISH, SUNFISH, RAINBOWFISH); therefore, there are no data to show efficacy and safety in this patient population.

IV. FIREFISH is an open-label, two-part study designed to assess safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). The study included 21 patients in Part One and 41 patients in Part Two aged one to seven months with Type I SMA. The following endpoints were used: Bayley Scales of Infant Development—Third Edition (BSID-III) Item 22, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Hammersmith Infant Neurologic Exam (HINE).

- BSID-III is a clinical evaluation developed to help identify children with developmental delay who may require intervention services. The BSID-III consists of three areas of development: cognitive, language, and motor. Effectiveness was established based on the ability to sit without support for at least five seconds (as measured by Item 22). This scale is intended for pediatrics only and is not specific to SMA.

- CHOP-INTEND is a validated, 16-item, 64-point scale, designed to measure motor function for weak infants with Type I SMA and is intended for pediatrics only. It measures spontaneous upper and lower extremity movement, hand grip, head in midline with visual stimulation, hip adductors, rolling from legs and arms, shoulder and elbow flexion by itself and in addition to horizontal abduction, knee extension, hip flexion an foot dorsiflexion, head control, head/neck extension, and spinal incurvation. Each of the 16 items is graded on a scale of zero to four, with zero meaning no response and four meaning complete response.

- HINE-2 is an SMA-specific measurement, 8-item, 26-point scale, designed to measure motor skills in infants with SMA. A score of zero for items such as sitting, crawling, and walking is expected for Type I. It measures voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking.

- The primary efficacy outcome in FIREFISH Part One was dose determination for Part Two of the study, which was 0.2 mg/kg/day. The primary efficacy outcome in FIREFISH Part Two was the proportion of infants sitting without support for at least five seconds as assessed by the Gross Motor Scale of the BSID-III at Month 12, which was 29% (90% CI: 17.8 to 43.1%). Key secondary efficacy outcomes in FIREFISH Part One include BSID-III at Month 12, which was 33%; infants alive with no permanent ventilation, 90.5%; proportion of infants who require hospitalization, and 38% did not require hospitalization. Key secondary efficacy outcomes in FIREFISH Part Two include HINE-2, which was 78% (p<0.0001) while the proportion of patients who achieved at least four points on the CHOP-INTEND score was 90% (p<0.0001).
V. SUNFISH is a two-part randomized, placebo-controlled study designed to assess safety, tolerability, efficacy, PK, and PD. The study included 51 patients in Part One and 180 patients in Part Two aged two to 25 with Type II or III SMA. Patients in Part Two of SUNFISH were randomized. The following endpoints were used: Motor Function Measure 32 (MFM-32) and Revised Upper Limb Module (RULM).

- MFM-32 is a 32-item scale that measures motor function abilities that relate to daily functions. The total MFM-32 score is expressed as a percentage (range: zero to 100) of the maximum possible score, with higher scores indicating greater motor function. This scale is suitable for assessing gross and fine motor skills in children and adult patients.

- RULM is a 19-item scorable scale used to assess motor performance of the upper limb in ambulatory and non-ambulatory patients with SMA. It tests proximal and distal motor functions of both upper limbs. The total score ranges from zero (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers). Each item is scored from zero to two: zero = unable, one = able with modification, two = able with no difficulty. RULM is applicable to both children and adults with SMA.

- The primary efficacy outcome in SUNFISH Part Two was the change from baseline to Month 12 in the MFM32 score in risdiplam (Evrysdi) vs. placebo, which was 1.36 (95% CI 0.61, 2.11) vs. -0.19 (-1.22, 0.84), with a difference from placebo of 1.55 (95% CI 0.30, 2.81, p=0.0156). Key secondary outcomes in SUNFISH Part Two include the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score in risdiplam (Evrysdi) vs. placebo, which was 38.3% (28.9, 47.6) vs. 23.7% (12.0, 35.4), with a difference from placebo of 2.35 (1.01, 5.44), p-value=0.0469; change from baseline in total score of RULM at Month 12 in risdiplam (Evrysdi) vs. placebo of 1.61 (1.00, 2.22) vs. 0.02 (-0.83, 0.87), with a difference from placebo of 1.59 (0.55, 2.62), p-value=0.0469.

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

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

- A total of 26 patients with pre-symptomatic SMA are currently enrolled and preliminary data (data cut off July 2021) is available for 7 patients (four patients had
2 copies of the SMN2, two patients had 3 copies, and one patient had >4 copies) treated with risdiplam (Evrysdi) for at least 12 months. Interim efficacy data showed patients treated with risdiplam (Evrysdi) achieved motor milestones (measured by the HINE-2) within WHO windows for healthy children at 12 months. All seven patients were alive at 12 months without permanent ventilation, achieved sitting without support, were able to feed exclusively by mouth, and maintained the ability to swallow solid food. In the six patients with two or three copies of the SMN2 genes, four patients (67%) were able to stand and 3 patients (50%) were able to walk independently at month 12. Interim safety data is consistent with the safety profile of risdiplam (Evrysdi) for pediatric and adult patients with symptomatic SMA. The most common adverse events included teething (33%), nasal congestion (28%), and pyrexia (28%). There were no reported deaths or treatment-related adverse events that led to withdrawal at data cut off. No treatment related serious adverse events were reported in patients treated for up to 22.8 months. Full efficacy and safety data RAINBOWFISH has not been published.

VIII. Baseline documentation of motor function/milestones for patients younger than 2 months of age proactively requesting risdiplam (Evrysdi) may not be available at the time of the request. To avoid delaying access to initial therapy in recently diagnosed infants, assessments completed shortly posttherapy may serve as baseline.

IX. Other acceptable motor measurements not measured in risdiplam (Evrysdi) trials, but are validated are the following: Hammersmith Functional Motor Scale Expanded (HFMSE) and Six-Minute Walk Test (6MWT)

- HFMSE is a 33-item scorable scale used to assess motor function in people with SMA Type II or Type III; this is intended for individuals older than 24 months of age. Each item is scored from zero (lowest item grade) to two (highest item grade), with a maximum score of 66. Higher scores indicate increased levels of ability. Scorable items include, but not limited to, plinth/chair sitting, long sitting, one to two hands to head in sitting, spine to side-lying, rolls prone to supine over right and left, rolls supine to prone over right and left, sitting to lying, props on forearms, lifts head from prone, prop on extended arms, lying to sitting, 4-point kneeling, crawling, and stepping.

- 6MWT is an objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type II or Type III) SMA. This test is based on distance where the patient walks as far as possible in six minutes; test is performed on a linear 25-meter marked course.

X. As of June 2022, the International Conference on the Standard of Care for Spinal Muscular Atrophy guidelines have not been updated to include risdiplam (Evrysdi) for the treatment of SMA.

XI. Per the Working Group for SMA-positive infants (comprised of 15 SMA experts), a pediatrician’s expertise in child healthcare may be broad and not cover the unique features of a rare neuromuscular disorder; similarly, a general child neurologist may not specialize in the role of the neuromuscular system of the patient’s symptomatology and diagnosis and may not have the knowledge to administer the specific tests being recommended here. A neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to
detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function.

XII. Nusinersen (Spinraza) is a chronic, intrathecally administered therapy. Use of risdiplam (Evrysdi) in patients (1-60 years of age) previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma) is currently being studied (JEWELFISH trial). Interim exploratory efficacy data suggest stabilization in motor function measured by change from baseline in motor function measure (MFM-32) at 12 months of treatment and the overall adverse event profile of risdiplam (Evrysdi) has been consistent with that in treatment naïve patients. At this time, there is no evidence to suggest efficacy and safety concerns of risdiplam (Evrysdi) in patients previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma).

XIII. Onasemnogene abeparvovec-xioi (Zolgensma) is a one-dose treatment and it is not a cure. Patients who previously received onasemnogene abeparvovec-xioi (Zolgensma) may continue to show signs and symptoms of SMA. Clinical deterioration is defined as, but not limited to, sustained decrease in CHOP-INTEND score over a period of six months (primary endpoint in the onasemnogene abeparvovec-xioi (Zolgensma) pivotal trial), increased frequency of breathing support (e.g., BiPAP machine at night, cough assist machine), and/or requirement of feeding tubes.

Investigational Uses

I. Risdiplam (Evrysdi) has not been FDA approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use in members with Type IV SMA
      i. Risdiplam (Evrysdi) has not been studied in this population.
   B. Use in combination with nusinersen (Spinraza)
      i. Risdiplam (Evrysdi) has not been studied as combination use with nusinersen.

Appendix

I. There are no specific contraindications or warnings and precautions to using risdiplam (Evrysdi)

II. Table 1: risdiplam (Evrysdi) Adult and Pediatric Dosing Regimen by Age and Body Weight

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<thead>
<tr>
<th>Age and Body Weight</th>
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<td>Less than 2 months of age</td>
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<td>2 months to less than 2 years of age</td>
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<td>2 years of age and older weighing less than 20 kg</td>
<td>0.25 mg/kg</td>
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<tr>
<td>2 years of age and older weighing 20 kg or more</td>
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References


**Related Policies**

*Currently there are no related policies.*

**Policy Implementation/Update**

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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>Updated criteria to include coverage in pre-symptomatic patients with two or three copies of SMN2 gene. Removed use in pre-symptomatic patients from E/I. Updated supporting evidence and references section.</td>
<td>06/2022</td>
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<tr>
<td>Policy created</td>
<td>11/2020</td>
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</tbody>
</table>
Policy Type: PA  
Pharmacy Coverage Policy: UMP105

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

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

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

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

Initial Evaluation

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

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

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

Supporting Evidence
I. Roflumilast (Daliresp) starting dose is 250 mcg per day to improve tolerability and reduce likelihood of discontinuation due to adverse effects; however, this dose is subtherapeutic. The 250 mcg tablets are administered once daily for four weeks; thereafter, 500 mcg daily is used for maintenance. A 250mcg daily maintenance or quantity exceptions to utilize two x 250 mcg tablets daily are not covered. The 500mcg tablet is administered once daily and has an extended half-life, eliminating the need for twice daily dosing. Additionally, the 500mcg tablet is more cost efficient.
II. Roflumilast (Daliresp) is indicated to reduce the risk of COPD exacerbations in patients with severe or very severe COPD associated with chronic bronchitis and have a history of exacerbations. It has only been evaluated in adults; safety and efficacy are unknown when used in pediatrics. COPD does not normally occur in children and rare cases may be due to genetic conditions; however, roflumilast (Daliresp) has unknown consequences in these settings.
III. Chronic bronchitis is defined as chronic productive cough for three months in each of two successive years in a patient whom other causes of chronic cough have been excluded.
IV. Effects of roflumilast (Daliresp) have been evaluated in nine phase 3 clinical trials and other supplemental studies. The majority of trials failed to show clinical improvement in lung function, exacerbation rate, survival, or quality of life in the general COPD population. Exploratory analyses of early clinical trials identified a subpopulation of patients that appeared to demonstrate a better response to roflumilast (Daliresp); those with severe COPD associated with chronic bronchitis that have a history of COPD exacerbations within the last year. Several clinical trials have demonstrated lack of clinical benefit of roflumilast (Daliresp) in an unselected patient population with COPD. Given the lack of benefit outside of the FDA-approved population coupled with specific safety concerns (e.g., psychiatric adverse effects including but not limited to suicide and suicidal ideation), coverage is limited to a narrow population.
V. The FDA-approval for roflumilast (Daliresp) is based on trials five and six of the clinical program that demonstrated a modest reduction in exacerbations vs. placebo and a statistically significant, but non-clinically significant, increase in FEV1. Patients were allowed to be on LABA or short-acting muscarinic antagonist (SAMA) therapy, and all patients had at least one recorded exacerbation requiring systemic corticosteroids or hospital admission within the previous year.

VI. A Cochrane Systematic Review of PDE4 inhibitors for COPD was conducted in 2020 to evaluate the extensive evidence for roflumilast (Daliresp) and other non FDA-approved therapies in this class. The conclusions of the review are as follows: PDE4 inhibitors in people with COPD may have additional but limited value and act independently of bronchodilators in patients with COPD. These therapies have a small benefit over placebo in reducing lung function or reducing likelihood of exacerbations. There is no known impact on quality of life or symptom control; however, there is cautious support for use and the identified place in therapy is as add-on therapy for patients with persistent symptoms or exacerbations despite optimal COPD management.

VII. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report stance: roflumilast (Daliresp) may reduce exacerbation rates in those with severe or very severe COPD with chronic bronchitis and a history of exacerbations – mirroring the FDA approved indication. It is noted that roflumilast (Daliresp) benefits may be greater in patients with a prior hospitalization for acute COPD exacerbation; however, it is unknown if the benefit is selective to those with prior exacerbation requiring hospitalization (subgroup analyses of trials signal a greater benefit in those with prior hospitalization). The GOLD report recommends the following therapy in patients with persistent exacerbations despite long-acting bronchodilator monotherapy:

- Escalate to LABA/LAMA or LABA/ICS unless eosinophil level is < 100 cells/μL.
- In those with exacerbation while on LABA/ICS: add a LAMA or switch to LABA/LAMA.
- In those with exacerbation on either triple therapy LABA/LAMA/ICS or in those with exacerbation on dual therapy with LABA/LAMA for which ICS was inappropriate: roflumilast (Daliresp) may be added in the setting of severe or very severe disease, chronic bronchitis, and if patients have a history of exacerbation; particularly in those that have been hospitalized for an exacerbation in the previous year.

VIII. The Canadian Thoracic Society and European Respiratory Society/American Thoracic Society guidelines provide similar recommendations for use or roflumilast (Daliresp). Roflumilast (Daliresp) is not a bronchodilator therapy and should not be used for the relief of acute bronchospasm. It is not recommended to be used as monotherapy given lack of benefit in symptom control or quality of life, and the medication has unknown effects on exacerbation rate when used alone. It is recommended that dual or triple therapy be used prior to initiation of roflumilast (Daliresp) and that at least one bronchodilator (LABA and/or LAMA) be continued with roflumilast (Daliresp). It is also appropriate for roflumilast (Daliresp) to be added to triple therapy (LABA/LAMA/ICS). Some evidence suggests that roflumilast (Daliresp) may have additive effects with ICS; however, ICS may not be appropriate for all patients (e.g., not tolerated, low eosinophil level). When eosinophil levels are < 100 cells/μL, it is unlikely that ICS will be an effective therapy for patients with COPD and is not a required therapy under this condition. When eosinophil level is adequate and tolerated, ICS is guideline recommended therapy prior to treatment initiation with roflumilast (Daliresp).
Investigational or Not Medically Necessary Uses

I. Roflumilast (Daliresp) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below and are considered experimental and investigational:
   A. Pediatric COPD
   B. Asthma

II. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability is considered not medically necessary. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

Appendix

I. GOLD Classification of Airflow Limitation Severity in COPD
   A. GOLD 1: Mild COPD, FEV1 is ≥ 80% predicted
   B. GOLD 2: Moderate COPD, FEV1 is ≥ 50% predicted but < 80% predicted
   C. GOLD 3: Severe COPD, FEV1 is ≥ 30% predicted but <50 predicted
   D. GOLD 4: Very Severe COPD, FEV1 is < 30% predicted

II. Long-acting beta agonists (LABA):
   A. Formoterol (Foradil Aerolizer)
   B. Salmeterol (Serevent Diskus)
   C. Olodaterol (Striverdi Respimat)
   D. Formoterol (Performist)
   E. Arformoterol (Brovana)
   F. May also be a part of combination inhalers: budesonide/formoterol (Symbicort), fluticasone/umeclidinium/vilanterol (Trelegy Ellipta), budesonide/glycopyrrolate/formoterol (Breztri Aerosphere), fluticasone/salmeterol (Advair, AirDuo, generic), fluticasone/vilanterol (Breo Ellipta), etc.

III. Long-acting muscarinic antagonists (LAMA):
   A. Umeclidinium (Incruse Ellipta)
   B. Glycopyrrolate (Seebri Neohaler, Lonhala), aclidinium (Tudorza Pressair), tiotropium (Spiriva)
   C. May also be a part of combination inhalers: umeclidinium/vilanterol (Anoro), tiotropium/olodaterol (Stiolto), glycopyrrolate/formoterol (Vevespi), and glycopyrronium/indacaterol (Ultibron), etc.

IV. Inhaled corticosteroids (ICS)
   A. Mometasone (Asmanex)
   B. Beclomethasone (Qvar)
   C. Budesonide (Pulmicort)
   D. Fluticasone (Flovent, Armonair)
   E. May also be part of combination inhalers, see above, etc.

Related Policies
Currently there are no related policies.
References


Policy Implementation/Update

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allowance of 250 mcg dose limited to one month titration period; Removal of requirement of recent hospitalization; Reworded to include very severe COPD patients for coverage allowance; Update to allow bypassing of ICS when eosinophil level is &lt; 100 cells/ul; Updated to require continuation of a long-acting bronchodilator; Removal of requirement to continue ICS; Addition of adult age requirement. Policy updated to current format with inclusion of supplementary sections: E/I, NMN, Appendix, Related Policies. Added detailed supporting evidence.</td>
<td>08/2022</td>
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<td>Criteria transitioned to policy format, with the following changes: further clarification around severe COPD definition, dose limit that it does not exceed 500 mcg per day if request is for a dose increase, supporting evidences were updated, and GOLD 2020 Report was updated.</td>
<td>11/2019</td>
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<tr>
<td>Criteria created</td>
<td>04/2018</td>
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</table>
ropeginterferon alfa-2b-njft (Besremi®)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP257

Split Fill Management*

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

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ropeginterferon alfa-2b-njft (Besremi)</td>
<td>500 µg/mL pre-filled syringe (PFS)</td>
<td>Polycythemia Vera (PV)</td>
<td>2 syringes/28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

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

II. **Ropeginterferon alfa-2b-njft (Besremi)** is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Myelofibrosis

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.

September 01, 2022
B. Essential thrombocythemia  
C. Chronic hepatitis infection (e.g., hepatitis B, hepatitis C)  
D. Acute myeloid leukemia (AML)  

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

**Supporting Evidence**  
I. **RIFN-α-2b (Besremi)** is FDA-approved for the treatment of adult patients with PV. PV is a rare, chronic, myeloproliferative disorder caused by a mutation in bone marrow stem cells resulting in blood cell overproduction. Symptoms include pruritis, fatigue, and microcirculatory disturbance. PV may progress to myelofibrosis and acute myeloid leukemia (AML).  
II. PV risk stratification is based on age and comorbidities. Patients ≥ 60 years at initial diagnosis and presence of cardiovascular comorbidities or thromboembolic event history are classified as high-risk. Risk level guides treatment. For low-risk PV, periodic phlebotomy combined with low-dose aspirin remain the first-line therapy. Patients with high-risk PV may require cytoreductive therapy. Additionally, low-risk PV patients, who are symptomatic after repeated phlebotomy may be considered as potential candidates for cytoreductive therapy. This may consist of patients who experience new thrombosis, splenomegaly, progressive thrombocytosis, or disease-related major bleeding event when being managed via phlebotomy. These patients, even though classified as low-risk PV cases, are recommended to be treated similar to high-risk PV. Cytoreductive therapy may be considered medically necessary in this subgroup of patients.  
III. The National Comprehensive Cancer Network (NCCN) guideline for the treatment of myeloproliferative neoplasms recommend hydroxyurea (HU) or peginterferon alfa-2a (Pegasys) as preferred cytoreductive agents. In practice, peginterferon alfa-2a (Pegasys) may be considered for younger patients, during pregnancy or where treatment with HU is contraindicated. For patients with intolerance or resistance to other cytoreductive agents, ruxolitinib (Jakafi) is a recommended subsequent-line therapy. As of March 2022, the NCCN guideline added RIFN-α-2b (Besremi) as ‘other recommended regimen’ (Category 2A) for the treatment of high-risk PV. Additionally, RIFN-α-2b (Besremi) may also be considered as another recommended regimen, when used adjunct to phlebotomy, for the initial treatment of low-risk PV. This recommendation is based on lower-level evidence (Category 2B). Current clinical data for RIFN-α-2b (Besremi) does not provide a high degree of confidence for use in the initial treatment of patients with low-risk PV, and cytoreductive treatment naive patients.  
IV. FDA-approval is based on efficacy data from a single-arm, open-label Phase 1/2 clinical trial (PEGINVERA) and safety profile assessed via subsequent open-label, randomized, active-controlled Phase 3 trials (PROUD-PV, CONTINUATION-PV) in addition to PEGINVERA.
- **Phase 1/2 study**: patients (N=51) were newly diagnosed, had exposure to HU, any risk level disease, and refractory to phlebotomy. RIFN-α-2b (Besremi) led to an overall hematological response of 75% at week 10, with 26% reported as complete response (CR). Additionally, 74% patients achieved a Hct ≤ 45% at 12 months.

- **Phase 3 trials**: Two concurrent randomized Phase3I trials assessed RIFN-α-2b (Besremi) versus standard therapy (HU): PROUD-PV to assess non-inferiority of RIFN-α-2b (Besremi) to HU over 12 month regimen; CONTINUATION-PV: to assess CHR and improvement in disease burden at 36 months of therapy. Primary endpoint results for these trials were not statistically significant and non-inferiority to HU was not shown. However, RIFN-α-2b (Besremi) improved long-term disease response and CHR at 36 months vs. HU.

V. Prescribing information for RIFN-α-2b (Besremi) includes a black box warning for fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.

VI. For those with high-risk PV and require cytoreductive therapy, HU is the preferred first-line therapy given the extensive history of use, established safety profile, efficacy and cost-effectiveness. Although not FDA-approved for the treatment of PV, peginterferon alfa-2a (Pegasys) has found its place as an alternative cytoreductive agent, with supportive data from multiple clinical trials and retrospective studies. Notably, a Phase 2 open-label clinical trial assessed Pegasy for induction of CR and PR in patients with high-risk PV (n=50), where in overall response rate of 60% (22% CR) was reported. Additional Phase 3 clinical trial (N=168) also assessed efficacy of Pegassy vs. hydroxyurea and reported comparable response rates.

VII. Currently available clinical data does not conclusively establish superiority of RIFN-α-2b (Besremi) over HU. Although RIFN-α-2b (Besremi) is purported to provide better acute tolerability due to longer interval between injections (14 days) versus Pegasys (7 days), efficacy and safety of RIFN-α-2b (Besremi) has not been compared with peginterferon alfa-2a (Pegasys) in a head-to-head clinical trial. At this time, real-world safety profile and patient experience with RIFN-α-2b (Besremi) remain largely unknown. Thus, preference toward bi-weekly dosing or convenience of administration does not establish medical necessity of RIFN-α-2b (Besremi) over peginterferon alfa-2a (Pegasys). Weighing the safety, efficacy, cost, and clinical experience, HU and peginterferon alfa-2a (Pegasys) are considered standard and appropriate high-value cytoreductive treatment options for the treatment of PV.

**Investigational or Not Medically Necessary Uses**

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

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

Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
References


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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<tr>
<th>Policy Name</th>
<th>Disease state</th>
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<tbody>
<tr>
<td>peginterferon alfa-2a (Pegasys)</td>
<td>Polycythemia vera</td>
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<tr>
<td></td>
<td>Essential thrombocytopenia</td>
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<tr>
<td></td>
<td>Chronic hepatitis B</td>
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<td>Chronic hepatitis D</td>
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Policy Implementation/Update:

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<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Policy created</td>
<td>05/2022</td>
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</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP152

Split Fill Management*

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>rucaparib (Rubraca)</td>
<td>200 mg tablets</td>
<td>Maintenance for: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;</td>
<td>120 tablets/30 days</td>
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<tr>
<td></td>
<td>250 mg tablets</td>
<td>Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg tablets</td>
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</table>

Initial Evaluation

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

*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.
v. Provider attests with supporting documentation that member’s recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen; OR

2. Advanced ovarian, fallopian tube, or primary peritoneal cancer; AND
   i. Provider is requesting for treatment therapy, and not maintenance therapy; AND
   ii. Member has been treated with two or more prior lines of chemotherapy; AND
   iii. Member has deleterious BRCA mutation (germline and/or somatic) confirmed by an FDA-approved compendia diagnostic for rucaparib (Rubraca).

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

Renewal Evaluation

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

Supporting Evidence

I. The safety and efficacy of rucaparib (Rubraca) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, multicenter trial (ARIEL3) where 564 adult patients with platinum-sensitive recurrent epithelial ovarian fallopian tube or primary peritoneal cancer. The patients were randomized 2:1 rucaparib (Rubraca) 600 mg orally daily or matched placebo within 8 weeks of their last dose of platinum-based therapy. The major efficacy outcome was progression-free survival (PFS) assessed by investigator, which ARIEL 3 demonstrated a statistically significant improvement in PFS in the rucaparib (Rubraca) arm as compared to the placebo arm.
rucaparib (Rubraca) arm, the median PFS was 10.8 months compared to 5.4 months in the placebo arm with a hazard ratio (HR) of 0.36 and 95% CI (0.3, 0.45).

II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e., as close to 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.

III. The safety and efficacy of rucaparib (Rubraca) for the treatment of advanced ovarian cancer after two or more chemotherapies was studied in two multicenter, single-arm, and open-label trials with 106 adult patients that have advanced BRCA-mutant ovarian cancer who had progressed after two or more prior chemotherapies. The efficacy outcomes were objective response rate (ORR) and duration of response (DOR) assessed by the investigator and independent radiology review; the average ORR was 54% and the average DOR was 9.2 months.

IV. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

**Investigational or Not Medically Necessary Uses**

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of rucaparib (Rubraca) in the following settings listed below:

   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Solid Tumors
   D. Prostate Cancer

   1. Efficacy of rucaparib (Rubraca) was investigated in an ongoing multi-center, single arm clinical trial (TRITON2) in patients with BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC), who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic BRCA mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline. Patients received rucaparib (Rubraca) 600 mg orally twice daily along with concomitant GnRH analog or had prior bilateral orchiectomy. Objective response rate (ORR) and duration of response (DOR) were assessed in patients with measurable disease by blinded IRR and by the investigator protocol. An ORR of 43.5% (n= 27; 31.0-56.7) was reported for IRR evaluation of 62 patients with measurable disease, while DoR was not estimable given the lack of data maturity. Quality of clinical evidence is low due to open label, single-arm trial design and lack of measurable survival outcomes and patient quality of life related outcomes. Of note, as of October 2020, rucaparib (Rubraca) is being studied in a phase 3 trial for mCRPC with other therapeutic agent(s) as active comparator (TRITON3) and results for this study are not available. Of note, another PARP-inhibitor, olaparib (Lynparza) is FDA-approved for treatment of mCRPC in patients who progressed on previous chemotherapy. Olaparib (Lynparza) was approved for this indication based on an open label phase 3 trial, which reported
survival outcomes (rPFS and OS) and has a category 1 recommendation per NCCN guidelines for treatment of prostate cancer.

* 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added split fill restriction given dose interruption/dose reduction rates. Corrected published QL to reflect 120/30. Confirmation of monotherapy use upon renewal.</td>
<td>08/2021</td>
</tr>
<tr>
<td>Updated supporting evidence for investigational use of rucaparib (Rubraca) for treatment of prostate cancer</td>
<td>11/2020</td>
</tr>
<tr>
<td>Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy), included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.</td>
<td>12/2019</td>
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</tbody>
</table>
Policy Type: PA (Jakafi SP)  Pharmacy Coverage Policy: UMP057

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

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

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

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

Initial Evaluation

I. Ruxolitinib (Jakafi) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, dermatologist, or immunologist; AND
   B. A diagnosis of one of the following:

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.
1. **Intermediate-to-high-risk myelofibrosis (MF)** which includes primary MF, post-polycythemia vera MF, or post essential thrombocytopenia MF; **OR**

2. **Polycythemia vera; AND**
   i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; **OR**

3. **Graft versus-host disease (GVHD), acute or chronic; AND**
   i. Member is 12 years of age or older; **AND**
   ii. Documentation of moderate-to-severe GVHD (e.g., Grade 2 to 4 GVHD, OR Grade B to D); **AND**
   iii. The member has had an inadequate response to steroids (e.g., prednisone, methylprednisolone, beclomethasone, budesonide).

II. **Ruxolitinib (Opzelura)** may be considered medically necessary when the following criteria are met:

   A. **Member has a diagnosis of atopic dermatitis; AND**
   B. **Member is 12 years of age or older; AND**
   C. **Treatment with at least one agent in ALL of the following groups have been ineffective, contraindicated, or not tolerated:**
      1. **Group 1: topical corticosteroids** (e.g., hydrocortisone, desonide, triamcinolone, betamethasone, clobetasol)**
      2. **Group 2: topical calcineurin inhibitors:** tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel)**
      3. **Group 3: topical phosphodiesterase 4 inhibitor:** crisaborole (Eucrisa); **AND**
   D. **Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors** (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib).

III. **Ruxolitinib (Jakafi, Opzelura)** is considered investigational when used for all other conditions, including but **not limited to:**

   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19
   D. Alopecia areata
   E. Vitiligo
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Malignancy or cancer outside of myelofibrosis

**Renewal Evaluation**

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

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

*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.*
III. For intermediate- to high-risk myelofibrosis (MF) OR polycythemia vera:
   A. Request is for ruxolitinib (Jakafi); AND
      1. Documentation of reduction in spleen volume; OR
      2. Provider attestation of positive treatment response (e.g., improvement in symptoms, hematocrit control); OR

IV. For graft versus-host disease (GVHD), acute or chronic:
   A. Request if for ruxolitinib (Jakafi); AND
      1. Provider attestation of positive treatment response (e.g. reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary); OR

V. For atopic dermatitis:
   A. Request is for ruxolitinib (Opzelura) topical treatment:
      1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, reduction in BSA involvement, pruritus symptom reduction); AND
      2. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib).

Supporting Evidence

I. Length of authorization for initial approval is six months due to the clinical trial design, efficacy was evaluated at 24 weeks or less for all indications. Additionally, therapy beyond six months of treatment should be reserved for those where benefits outweigh the risks. For ruxolitinib (Jakafi) if no treatment response is seen at six months, therapy should be tapered into discontinuation. Therapy should not be abruptly discontinued given the potential for symptom proliferation and exacerbation.

II. The FDA-approved conditions for this therapy require specialized and individualized care and monitoring; thus, a specialist prescriber, or consultation with a specialist, is required.

III. Treatment for MF is based on risk. For intermediate-to high risk MF, stem cell transplant is the recommended treatment option; however, for those ineligible for stem cell transplant, hydroxyurea, fedratinib (Inrebic), and ruxolitinib (Jakafi) are available treatment options. While hydroxyurea may relieve splenomegaly and some symptoms of the condition (e.g., thrombocytosis, leukocytosis), it is thought to be less efficacious than other treatment options and may not be beneficial for major symptoms of the condition.

IV. Polycythemia vera treatment selection is also based on risk. Phlebotomy and/or low-dose aspirin are used in the management of low-risk disease. For high-risk disease, hydroxyurea is the preferred therapy given the extensive history of use, well-established safety profile, efficacy, and cost-effectiveness. Although busulfan has been used historically as a second-line therapy, because it has been associated with safety concerns such as cytopenia, pulmonary fibrosis, leukemia, and others, hydroxyurea remains the mainstay therapy. Ruxolitinib (Jakafi) is reserved for those that are not candidates for, or are refractory to, hydroxyurea, given the limited long-term safety and efficacy data. Additionally, for the treatment of polycythemia vera, ruxolitinib (Jakafi) is specifically FDA-approved after inadequate response or intolerance to hydroxyurea.

V. The FDA approval of ruxolitinib (Jakafi) in the setting of intermediate-to high-risk myelofibrosis was based on the results of two randomized Phase 3 trials. In Study 1, the primary endpoint was
the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 24. Secondary outcomes included proportion of patients achieving a 50% or greater reduction in Total Symptom Score from baseline to week 24. This was measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF), which incorporates abdominal discomfort, pain, night sweating, itching, bone and muscle pain, and early satiety. The study met statistical significance in all outcomes. In Study 2, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 48. This outcome was statistically significant.

VI. The FDA approval of ruxolitinib (Jakafi) in the setting of polycythemia vera was based on the result of a randomized, open-label, active-controlled Phase 3 study. The primary endpoint was the proportion of participants at Week 32 achieving hematocrit control in the absence of phlebotomy and spleen volume reduction. In the ruxolitinib (Jakafi) arm, 60% of the participants met the primary endpoint compared to 19% in the placebo arm. Participants must have had a resistance or intolerance to hydroxyurea.

VII. Graft-versus-host disease is a complication of allogenic hematopoietic cell transplant. Treatment is dependent on severity and location of disease. The GVHD Grade depends on severity and location, and ranges from I-IV. Grade I is reflective of skin involvement, Grade IV is severe disease with severe skin involvement (e.g., blistering) and internal organ involvement, and Grade II-IV correlate with moderate to severe disease. The International Bone Marrow Transplant Registry Severity Index uses Grade A-D, which align with grading I-IV.

VIII. For Grade I or A, or mild disease, topical therapy is indicated. For Grade II or B or greater, or moderate-to-severe disease, systemic therapy is warranted. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended as there is currently no consensus on standard of care. Otherwise, therapies such as ruxolitinib (Jakafi) or ibrutinib (Imbruvica) are recommended. Therapy such as mycophenolate, rituximab, etanercept (Enbrel), everolimus, and others have been used historically, but there is lack safety and efficacy data from clinical trials to support the use of these therapies.

IX. The FDA approval of ruxolitinib (Jakafi) in the setting of acute GVHD was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades II to IV that were 12 years of age or older. Therapy was evaluated up to 10 mg twice daily. The efficacy of ruxolitinib (Jakafi) was based on a Day-28 overall response rate (ORR) by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria and the duration of response. The ORR was 57.1% with a median duration response of 16 days.

X. For chronic GVHD, ruxolitinib (Jakafi) was evaluated in a Phase 3, open-label, randomized trial against best available treatment (BAT). Patients were 12 years of age or older, steroid-refractory, and had moderate-to-severe disease. Outcomes were ORR, failure-free survival (FFS), and Lee Symptom Score. Ruxolitinib (Jakafi) was superior to BAT in all outcomes. Given the availability of objective and subjective positive outcomes in this condition, and lack of standard of care beyond glucocorticoids, there is moderate confidence that ruxolitinib (Jakafi) provides clinical value for this condition.

XI. To date, ruxolitinib (Jakafi) has not been shown to improve survival for any condition.

XII. The safety and efficacy of ruxolitinib (Jakafi), or any other JAK inhibitor has not been evaluated in patients under 12 years of age.
XIII. Split fill applies to ruxolitinib (Jakafi) given the high rates of treatment discontinuation due to adverse events, and the rates of dose reduction or interruption seen in clinical trials (e.g., in the pivotal trial for aGVHD the rate of treatment discontinuation due to adverse events was 31%).

XIV. Topical ruxolitinib is the first non-oral JAK inhibitor for the treatment of atopic dermatitis (AD). Emerging data are showing JAK inhibitors to be effective therapies; however, competing JAK therapies are oral systemic treatments: abrocitinib, upadacitinib (Rinvoq), and baricitinib (Olumiant).

XV. Nonpharmacologic treatment options for mild-to-moderate AD include emollients, wet wrap therapy, and phototherapy. Topical pharmacologic treatment options include corticosteroids (TCS), calcineurin inhibitors (TCI) (e.g., tacrolimus, pimecrolimus), and phosphodiesterase-4 inhibitor crisaborole (Eucrisa). Choice of therapy is dependent on severity, location, and other patient factors (e.g., allergies, age).

XVI. Ruxolitinib (Opzelura) was evaluated in two Phase 3, randomized, double-blind, vehicle-controlled studies in 872 adolescents and adults (TRuE-AD1 and TRuE-AD2) age 12 and older. Treatment arms: vehicle, ruxolitinib 0.75% or 1.5%. Treatment was used continuously for eight weeks, then patients from the vehicle arm were re-randomized 1:1 to ruxolitinib 0.75% or ruxolitinib 1.5% for an additional 44 weeks. Trial population characteristics included: At least 12 years of age, 60% were female, 70% were white, had a mean affected BSA of 9-10%, baseline EASI of 8, 75% of patients had an IGA of 3, a mean NRS score of 5, median duration of AD of 16 years, and 40% of patients had facial involvement.

XVII. The primary outcome was proportion of patients achieving IGA treatment success (IGA-TS) (i.e., IGA score of 0 or 1 with at ≥ 2 grade improvement). Secondary outcomes were EASI75, change in EASI, and proportion of patients achieving ≥ 4-point improvement in the NRS itch score. At eight weeks, both ruxolitinib arms showed statistical and clinical superiority to vehicle in all outcomes. The 52-week assessments showed similar, or favorable outcomes.

XVIII. At eight weeks, rates of adverse events (AE) were similar among all treatment arms and were mild or moderate in severity. Common AE were burning (≤ 6.5%) and pruritis (3.2%). Discontinuation rates due to AE were ≤ 4%. Safety data out to 52 weeks did not reveal additional safety warnings. No serious AE occurred as a result of ruxolitinib (Opzelura) treatment; however, there was a relatively small patient population evaluated, and with data only out to 52 weeks there may be unrealized safety characteristics. Although two clinical trials showed consistent improvement in the outcomes noted above, there remains uncertainty in the following: place in therapy, safety and efficacy data when used in combination with other topical therapies and/or systemic treatments for AD, long term safety, durability of efficacy, and comparative efficacy to other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. Furthermore, there is lack of safety and efficacy data in pediatric patients under 12 years of age. Other topical therapies have been approved in this age group, and ruxolitinib is being evaluated in this population.

XIX. The safety profile of systemic JAKs is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib (Opzelura) is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use...
will be disallowed. For those in need of systemic and topical therapy, provider and patients should consider therapies and combination with alternative mechanisms, including, but not limited to, dupilumab, tralokinumab systemic therapies, and the aforementioned topical therapies.

XX. Ruxolitinib (Opzelura) 1.5% topical cream is FDA-approved at a maximum of 60 grams per week, and medication should not be applied to greater than 20% of the body surface area. Additionally, therapy should be used for short term and non-continuous treatment of mild to moderate atopic dermatitis. A quantity limit of two tubes (120 grams total) per 28-day supply should be sufficient or better for the majority of patients to utilize this therapy. Upon initial trial of medication, quantity limits will be set at two tubes per 28-day supply to ensure appropriate utilization within FDA label (e.g., non-continuous use), as well as ensure patients realize efficacy with medication and to minimize medication waste in the event therapy is not effective.

**Investigational or Not Medically Necessary Uses**

I. Ruxolitinib (Jakafi, Opzelura) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19 or associated symptoms or complications
   D. Alopecia areata
   E. Vitiligo
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Cancer or malignancy outside of myelofibrosis

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

**References**


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib cream added into the policy for the treatment of atopic dermatitis.</td>
<td>08/2021</td>
</tr>
<tr>
<td>Chronic graft vs. host disease indication added to policy. Update of qualifying prescribers and appropriate doses and quantities per indication. Removal of infection free requirement, check of unacceptable toxicity, and requirement for previous use of hydroxyurea in myelofibrosis.</td>
<td>06/2021</td>
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<tr>
<td>Addition of acute graft vs. host disease indication to renewal section.</td>
<td>01/2020</td>
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<tr>
<td>Criteria transitioned to policy. Added newly FDA approved indication of acute graft versus host disease. Remove diagnostic questions, interaction questions, lab value questions. Added requirement for previous use of hydroxyurea prior to coverage of Jakafi for the indication of polycythemia vera.</td>
<td>07/2019</td>
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<td>Previous reviews</td>
<td>12/2014, 12/2012, 07/2012, 05/2012</td>
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</tbody>
</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP209

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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

Initial Evaluation

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

II. Satralizumab (Enspryng) is considered not medically necessary when criteria above are not met and/or when used for:
   A. NMOSD that is anti-quaporin-4 (AQP4) IgG antibody negative (i.e., seronegative)

III. Satralizumab (Enspryng) is considered investigational when used for all other conditions, including but not limited to:
   A. Rheumatoid or other forms of arthritis
   B. Cytokine release syndrome
   C. Arteritis

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

Supporting Evidence
I. Satralizumab (Enspryng) is FDA-approved for NMOSD, a rare inflammatory disorder characterized by severe, immune-mediated attacks on the optic nerves and spinal cord. Hallmark features include optic neuritis attacks, transverse myelitis, unexplained hiccups, nausea, vomiting, and somnolence. Patients experience relapses that have varying degrees of recovery over weeks to months. NMOSD was historically considered as a form of multiple sclerosis (MS); however, MS therapies are often inefficacious in the setting of NMOSD and certain MS therapies may further exacerbate NMOSD. Thus, a definitive diagnosis from a specialty provider is warranted. The majority of patients are seropositive, and if test results show seronegative disease, patients should be retested or considered for a differential diagnosis. Seronegative disease is often treated similarly to seropositive NMOSD; however, biologic medications often lack efficacy in the seronegative population.

II. NMOSD is often treated acutely with high-dose IV glucocorticoids, and if refractory – plasma exchange. Once a definitive diagnosis is made, long-term therapy is recommended in all patients. Long-term therapies that are FDA-approved include eculizumab (Soliris) and inebilizumab (Uplinza), which are both provider administered products. Other therapies that
have been used historically and are often regarded as standard of care include glucocorticoids, azathioprine, mycophenolate, and rituximab (e.g., Rituxan). Additionally and increasingly, IV tocilizumab (Actemra) has been considered. The quality of data varies for these agents; however, all have shown positive response on relapse rates for seropositive NMOSD. The safety profile, is also further defined, given the longevity and extent of use in patients relative to satralizumab (Enspryng).

III. The efficacy and safety of satralizumab (Enspryng) was evaluated in two Phase 3, blinded, randomized, placebo-controlled trials, where treatment was administered at weeks zero, two, four, then four weeks thereafter. Population characteristics: seropositive and negative patients, majority female, an annualized relapse rate of 1.5 with at least one documented attack in the last 12 months, with a variety of treatment histories (e.g., glucocorticoids [GC], DMARDS, previous b-cell depleting therapy). Exclusions: history of anti-IL-6 therapy, alemtuzumab, total body irradiation, or bone marrow transplantation.

IV. Trial one evaluated satralizumab (Enspryng) monotherapy versus placebo, and trial two evaluated against placebo with both groups adding treatment to background immunosuppressive therapy (glucocorticoids, mycophenolate, azathioprine, and various combinations). The use of satralizumab (Enspryng) in addition to other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) has not been evaluated for safety and/or efficacy. Additionally, there is evidence to show that use of two biologic therapies concurrently has demonstrated increased risk of serious infection.

V. Adolescent patients were included in the second pivotal trial, ages 12 and older. There was a low number (n=7) enrolled and subgroup analyses did not show clinical efficacy. Although this analysis was likely underpowered, safety and efficacy in non-adult population remains unknown at this time and FDA-approval has been granted for adults only.

VI. In both trials there was a positive response on relapse rates in the seropositive (anti-aquaporin-4 [AQP4] antibody-positive) population. Of note, there was a lack of statistically significant efficacy in the seronegative population. Secondary outcomes evaluated medication efficacy on other symptom control, quality of life, and caregiver burden; however, they were not statistically significant. Medication success may be measured as a reduction in or freedom from relapses.

Investigational or Not Medically Necessary Uses

I. Satralizumab (Enspryng) did not show improvement in relapse rates in the seronegative NMOSD population. Given lack of efficacy and largely unknown safety profile for this therapy, use is not medically necessary at this time.

II. Satralizumab (Enspryng) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Rheumatoid or other forms of arthritis
   B. Cytokine release syndrome
   C. Arteritis
      i. IL-6 therapies (e.g., tocilizumab [Actemra] have been FDA-approved for the conditions listed above; however, use of satralizumab (Enspryng) for these conditions remains experimental and investigational.

Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
References


Policy Implementation/Update:

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<th>Date</th>
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<tr>
<td>Policy created</td>
<td>11/2020</td>
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Select Testosterone Products

Policy Type: PA

Pharmacy Coverage Policy: UMP067

Description
Testosterone is the primary endogenous androgen responsible for promoting growth and development of male sex organs and the maintenance of secondary sex characteristics.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>testosterone undecanoate (Jatenzo)</td>
<td>158 mg tablets</td>
<td></td>
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<td></td>
<td>198 mg tablets</td>
<td></td>
<td>120 capsules/30 days</td>
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<tr>
<td></td>
<td>237 mg capsules</td>
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<td>60 capsules/30 days</td>
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<td>testosterone undecanoate (Aveed)</td>
<td>750 mg/3 mL intramuscular solution</td>
<td></td>
<td>3 mL/28 days</td>
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<tr>
<td>testosterone (Striant)</td>
<td>30 mg buccal system</td>
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<td>60 buccal systems/30 days</td>
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<td>testosterone (Androderm)</td>
<td>2 mg/24 hour patch</td>
<td>Primary hypogonadism; hypogonadotropic hypogonadism</td>
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<td></td>
<td>4 mg/24 hour patch</td>
<td></td>
<td>30 patches/30 days</td>
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<td>testosterone 1% (AndroGel, Testim, Vogelxo)</td>
<td>25mg/2.5gm gel</td>
<td></td>
<td>300 g/30 days</td>
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<tr>
<td></td>
<td>50 mg/5gm gel</td>
<td></td>
<td>300 g/30 days</td>
</tr>
<tr>
<td></td>
<td>1.25 g/actuation gel pump</td>
<td></td>
<td>300 g/30 days</td>
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<tr>
<td>testosterone 1.62% (AndroGel, Vogelxo)</td>
<td>20.25 mg/ 1.25 gm gel packet</td>
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<td>150 g/30 days</td>
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<td></td>
<td>40.5 mg/2.5gm gel packet</td>
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<td>20.25 mg/actuation gel pump</td>
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<td>Drug</td>
<td>Dosage</td>
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<tr>
<td>Testosterone Cypionate (Depot-testosterone)</td>
<td>100mg/mL intramuscular injection</td>
<td>8 mL/28 days</td>
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<td>Testosterone Cypionate (Depot-testosterone)</td>
<td>200mg/mL intramuscular injection</td>
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<td>Testosterone (Axiron)</td>
<td>30 mg actuation roll-on solution</td>
<td>110 mL/30 days</td>
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<tr>
<td>Testosterone (Xyosted)</td>
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<td>Testosterone Cypionate 2% (Fortesta)</td>
<td>50 mg/0.5 mL subcutaneous solution autoinjector</td>
<td>5 mL/28 days</td>
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<td>75 mg/0.5 mL subcutaneous solution autoinjector</td>
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<td>100 mg/0.5 mL subcutaneous solution autoinjector</td>
<td>4 mL/28 days</td>
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<td>10mg/actuation gel</td>
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</tbody>
</table>

**Initial Evaluation**

I. Testosterone (Branded) may be considered medically necessary when the following criteria are met:

   A. A diagnosis of one of the following:
      1. **Gender dysphoria; OR**
      2. **Primary or Secondary Hypogonadism defined as one of the following;**
         i. Primary hypogonadism (testicular failure) due to Klinefelter syndrome (KS), cryptorchidism, orchiectomy, vanishing testes syndrome, chemotherapy affecting or radiation to the testes, testicular trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, or myotonic dystrophy; **OR**
         ii. Secondary hypogonadism (pituitary-hypothalamic hypogonadism) as caused by hypothalamic or pituitary tumor, iron overload syndromes,
idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, head trauma, or pituitary surgery or radiation; **AND**

iii. **Two** sub-normal testosterone concentration levels taken on **two** separate mornings while fasting; **AND**

iv. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
   a. Generic injectable testosterone; **AND**
   b. Generic topical testosterone; **AND**

v. Member is male; **AND**

vi. Age is 18 years old or greater; **AND**

vii. Member does **not**:
   a. Plan to conceive; **OR**
   b. Have breast or prostate cancer; **OR**
   c. Have palpable prostate nodule or induration; **OR**
   d. Have a prostate-specific antigen level greater than 4 ng/mL, a prostate-specific antigen greater than 3 ng/mL combined with a high risk of prostate cancer; **OR**
   e. Have testosterone levels within the normal range

II. **Testosterone is considered not medically necessary** when used for all other conditions, including
   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, present with testosterone level within normal range.

III. **Testosterone is considered investigational** when used for all other conditions, including but **not limited to**:
   A. Age-related hypogonadism
      1. The role of testosterone replacement to treat the natural decline in serum testosterone common in men over the age of 60, without identified pituitary or hypothalamic disease, is uncertain.
   B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
   C. For the healing of fracture
   D. Functional uterine bleed
   E. Treatment of weight loss unrelated to HIV-wasting

**Renewal Evaluation**

I. A previously approved prior-authorization for a branded testosterone product.

**Supporting Evidence**
I. 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.

II. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.

III. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.

IV. The benefit of increasing testosterone concentration has only been shown in patients with organic hypogonadism due to disorders of the hypothalamus, pituitary or testes.

V. 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. Due to this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

VI. To discriminate between primary and secondary hypogonadism, a measurement of serum luteinizing hormone (LH) and follicle-stimulation hormone (FSH) concentrations is required.
   - Primary: testicular failure; usually associated with high LH and FSH
   - Secondary: pituitary and/or hypothalamic dysfunction; usually associated with low LH and FSH

VII. Lower limit of the normal total testosterone (TT) to the CDC standard in healthy, non-obese young men is 264 ng/dL (9.2 nmol/L).

VIII. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of oral testosterone undecanoate (Jatenzo) or topical testosterone products in women.

IX. A randomized trial showed that use of testosterone undecanoate (Jatenzo) resulted in an increase in systolic and diastolic blood pressure by an average of 4.9 mmHg and 2.5 mmHg, respectively.
   - Increases in hematocrit and heart rate were also noted, leading to an increased risk of major adverse cardiac events (MACE), limiting dose frequency to twice daily.

X. Testosterone replacement therapy is subject to abuse at doses higher than recommended for approved indications and in combination with other anabolic androgenic steroids. Abuse-related adverse events include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, hepatotoxicity, and serious psychiatric complaints.

XI. Payment consideration for oral methyltestosterone is reserved for members who have tried and failed injectable testosterone. Testosterone enanthate injectable is approved for use in females that have 1-5 years postmenopausal advanced inoperable metastatic breast cancer, in premenopausal women who have benefited from oophorectomy with hormone responsive tumors, OR in delayed puberty in males. Topical formulations of testosterone are not indicated for use in women and pediatrics.
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.

References

Policy Implementation/Update:

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<tr>
<td>Last Updated</td>
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Action and Summary of Changes

| Change to policy format; added supplementary evidence section; updated references | 07/2018 |
| Add methyltestosterone to table; removed DDID column | 12/2019 |
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP086

Split Fill Management*

Description
Selinexor (Xpovio) is an oral nuclear export inhibitor.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
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<td>selinexor (Xpovio)</td>
<td>80 mg tablet twice weekly carton</td>
<td>Relapsed or refractory multiple myeloma (MM)</td>
<td>1 carton (32 tablets)/28 days</td>
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<tr>
<td></td>
<td>100 mg tablet once weekly carton</td>
<td></td>
<td>1 carton (20 tablets)/28 days</td>
</tr>
<tr>
<td></td>
<td>80 mg tablet once weekly carton</td>
<td></td>
<td>1 carton (16 tablets)/28 days</td>
</tr>
<tr>
<td></td>
<td>60 mg tablet once weekly carton</td>
<td></td>
<td>1 carton (12 tablets)/28 days</td>
</tr>
<tr>
<td></td>
<td>40 mg tablet once weekly carton</td>
<td></td>
<td>1 carton (8 tablets)/28 days</td>
</tr>
<tr>
<td></td>
<td>60 mg tablet twice weekly carton</td>
<td>Relapsed or refractory diffuse large B-cell</td>
<td>1 carton (24 tablets)/28 days</td>
</tr>
<tr>
<td></td>
<td>40 mg tablet twice weekly carton</td>
<td>lymphoma (DLBCL)</td>
<td>1 carton (16 tablets)/28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

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

II. Selinexor (Xpovio) is considered investigational when used for all other conditions, including but not limited to:
   A. Multiple myeloma when given as part of a quadruplet (“quad”) regimen
   B. Diffuse large B-cell lymphoma

Renewal Evaluation

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

Supporting Evidence

I. As of February 2021, selinexor (Xpovio) has three FDA-approved indications:
   • In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy
   • In combination with dexamethasone in adult patients with multiple myeloma who have previously received at least four prior therapies and whose disease is refractory to at
least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (penta-refractory)

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

II. Multiple myeloma (MM)

- Selinexor (Xpovio) is indicated for use in two different multiple myeloma settings: (1) received at least one prior therapy (BOSTON trial) and (2) received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (STORM trial).

- Selinexor (Xpovio) for treatment in the setting of penta-refractory MM was approved via the accelerated approval pathway, and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. Results from the BOSTON trial confirmed continued approval for use in the setting of penta-refractory MM.

i. STORM: Phase 2, open-label trial of 79 patients in combination with dexamethasone only. No other oncolytic therapies were included in the drug regimen. Patients included were previously treated with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb and refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

1. The primary endpoint was objective response rate (ORR), which occurred in 21%. Secondary outcomes included progression free survival (PFS) and overall survival (OS), which resulted in 2.3 and 9.3 months, respectively.

2. The safety profile is as follows: Sixty percent of patients in the trial experienced grade 3-4 adverse events including thrombocytopenia, anemia, and neutropenia. Additionally, other serious adverse events occurred such as febrile neutropenia, serious infections, and fatal serious bleeding.

3. Selinexor (Xpovio) has not been sufficiently studied in the penta-refractory setting with further clinical evaluation of safety and efficacy needed to confirm a net health benefit and place in therapy for this medication.

ii. BOSTON: Phase 3, randomized, open-label trial of 402 patients in combination with bortezomib and dexamethasone (N= 195 SEL-BTZ-Dex) compared to a combination with bortezomib and dexamethasone only (N=207 BTZ-Dex). Patients included had received one to three previous different regimens for multiple myeloma. Patients who previously received proteasome inhibitors (mono- or combination therapy) were required to have had at least a partial response and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3+ AEs.

1. The primary efficacy endpoint was progression free survival (PFS), which was 13.93 months in the SEL-BTZ-Dex arm versus 9.46 months in the BTZ-Dex arm. Key secondary endpoints were overall survival (OS), which was not reached in the SEL-BTZ-Dex arm versus 25 months in the BTZ-Dex arm; overall response rate (ORR) of 76.4% in the SEL-BTZ-Dex arm versus 62.3% in the BTZ-Dex arm; duration of response (DoR) of 20.3 months in the SEL-BTZ-
Dex arm versus 12.9 months in the BTZ-Dex arm; time to response (TTR) of 1.1 months in the SEL-BTZ-Dex arm versus 1.4 months in the BTZ-Dex arm.

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

- **Recommended dosage for MM:**
  i. In combination with bortezomib and dexamethasone is selinexor (Xpovio) 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity.
  ii. In combination with dexamethasone is selinexor (Xpovio) 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.

- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for previously treated multiple myeloma has included selinexor (Xpovio) in combination with bortezomib and dexamethasone as “Other Recommended Regimens” (Category 1 recommendation). Additionally, NCCN recommends selinexor (Xpovio) in combination with dexamethasone as “Useful in Certain Circumstances” for patients with relapsed/refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (Category 2A recommendation).

III. **Diffuse large B-cell lymphoma (DLBCL)**

- **SADAL:** Phase 2, an open-label, single-arm, multi-cohort trial of 127 patients with de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma, previously treated with two to five lines of therapy and progressed after, or were not candidates for autologous stem-cell transplantation were included. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. FDA approval was based on the overall response rate (ORR).
  i. The primary efficacy endpoint was overall response rate (ORR), which occurred in 28%, and the secondary endpoint was duration of response (DoR), which was 9.3 months. Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.
ii. Safety results were analyzed in all patients who received at least one dose of selinexor (Xpovio) (N=125). The most common adverse events (≥20% incidence) included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, constipation, neutropenia, weight loss, vomiting, pyrexia, and asthenia. There are no specific contraindications to selinexor (Xpovio); however, warnings and precautions include: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurological toxicity, and embryo-fetal toxicity. Selinexor (Xpovio) showed a 93% treatment discontinuation rate: 63% due to disease progression, 10% withdrawal by patient, 7% death, 6% physician decision, and 7% due to adverse events.

- Selinexor (Xpovio) for treatment in the setting of DLBCL received accelerated approval from the FDA based on ORR and DoR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 2/3 trial underway to assess rituximab + gemcitabine + dexamethasone + platinum (R-GDP) with or without selinexor (Xpovio) in patients with relapsed/refractory diffuse large B-cell lymphoma.
- Recommended dosage for DLBCL:
  i. Selinexor (Xpovio) 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for B-cell lymphomas has included selinexor (Xpovio) as third-line and subsequent treatment with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

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

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

Table 1: Classification of Medications used for Multiple Myeloma

<table>
<thead>
<tr>
<th>Proteasome Inhibitors</th>
<th>Immunomodulatory Agents</th>
<th>Monoclonal Antibodies</th>
<th>Histone Deacetylase Inhibitors</th>
<th>B-cell Maturation Antigen-Directed Antibody</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>bortezomib</td>
<td>thalidomide</td>
<td>elotuzumab</td>
<td>panobinostat</td>
<td>belantamab mafodotin-blfm</td>
<td>cyclophosphamide</td>
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<td>carfilzomib</td>
<td>lenalidomide</td>
<td>daratumumab</td>
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<td>doxorubicin</td>
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<td>ixazomib</td>
<td>pomalidomide</td>
<td>isatuximab-irfc</td>
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<td>etoposide</td>
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Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions

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


Policy Implementation/Update:

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<td>Added split fill management, length of authorization. Updated quantity limits to include 40 mg tablet once weekly carton, as well as DLBCL dosage forms. Updated penta-refractory MM indication from E/I to allow criteria coverage. Added criteria coverage for new MM indication of at least one prior therapy. Added new DLBCL indication and quad-regimen for MM as E/I. Added additional supporting evidence to include more details surrounding all three indications. Added “Table 1: Classification of Medications used for Multiple Myeloma” and “Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions” under Appendix.</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP192

Split Fill Management*

Description
Selpercatinib (Retevmo) is an orally administered kinase inhibitor of RET.

Length of Authorization
- N/A

Quantity Limits

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<tr>
<td>selpercatinib (Retevmo)</td>
<td>40 mg capsules</td>
<td>RET Fusion-Positive Non-Small Cell Lung Cancer</td>
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<td></td>
<td></td>
<td>RET-Mutant Medullary Thyroid Cancer</td>
<td></td>
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<tr>
<td></td>
<td>80 mg capsules</td>
<td>RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory</td>
<td>120 capsules/30 days</td>
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Initial Evaluation

I. Selpercatinib (Retevmo) is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Selpercatinib (Retevmo) is the first FDA-approved therapy that targets RET alterations specifically.

II. Selpercatinib (Retevmo) is a kinase inhibitor of RET. It is FDA-approved for adults with metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients age 12 years and older, and advanced or...
metastatic RET fusion-positive thyroid cancer who are radioactive iodine (RAI)-refractory in patients age 12 years and older.

III. RET fusion-positive NSCLC, advanced or metastatic: First-line treatment options include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (not FDA-approved for lung cancer) or combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed, and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine).

IV. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).

V. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, radioactive iodine (RAI) is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).

VI. Selpercatinib (Retevmo) is being evaluated in one Phase 1/2, open-label, multi-cohort, single-arm trial in patients with RET abnormal, advanced solid tumors. Interim results showed potential antitumor activity, based on objective response rate (ORR), in the three FDA-approved settings. Additional outcomes: progression-free survival (PFS) and overall survival (OS) at 12 months.

- RET fusion-positive NSCLC: Patients were advanced or metastatic, progressed on platinum-based chemotherapy or were systemic treatment naïve. Over half of pretreated patients also received anti-PD1/PD-L1 therapy (n=58).
- RET-mutant MTC: 98% had metastatic disease, and patients were previously treated with cabozantinib (Cometriq) and/or vandetanib (Caprelsa), or were treatment naïve to both. Ten patients were previously treated with platinum chemotherapy or anti-PD1/PD-L1 therapy.
- RET fusion-positive TC: Patients were not amenable to RAI therapy, and may have been treated with lenvatinib (Lenvima) and/or sorafenib (Nexavar), or were naïve to both.

<table>
<thead>
<tr>
<th>Clinical Efficacy in Pretreated Patients</th>
<th>Outcome</th>
<th>RET Fusion+ NSCLC (n=105)</th>
<th>RET-Mutant MTC (n=55)</th>
<th>RET Fusion-Positive TC (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (n)</td>
<td></td>
<td>67 (64%)</td>
<td>38 (69%)</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>CR (n)</td>
<td></td>
<td>2 (2%)</td>
<td>5 (9%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>PR (n)</td>
<td></td>
<td>65 (62%)</td>
<td>33 (60%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>PFS (months)</td>
<td></td>
<td>16.5 (13.7-NE)</td>
<td>NE</td>
<td>20 (9.4-NE)</td>
</tr>
<tr>
<td>OS, 12 months (%)</td>
<td></td>
<td>88%</td>
<td>87%</td>
<td>NR</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinical Efficacy in Treatment-Naïve Patients</th>
<th>Outcome</th>
<th>RET Fusion+ NSCLC (n=39)</th>
<th>RET-Mutant MTC (n=88)</th>
<th>RET Fusion-Positive TC (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (n)</td>
<td></td>
<td>33 (85%)</td>
<td>64 (73%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>CR (n)</td>
<td></td>
<td>0</td>
<td>10 (11%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>PR (n)</td>
<td></td>
<td>33 (85%)</td>
<td>54 (61%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>PFS (months)</td>
<td></td>
<td>NE</td>
<td>23.6 (NE-NE)</td>
<td>NE</td>
</tr>
<tr>
<td>OS, 12 months (%)</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

VII. Selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. This therapy is being evaluated in multiple other clinical Phase 2 and Phase 3 trials. The quality of the evidence is considered low at this time given the open-label...
trial design and lack of comparator arm. Given the observational data, medication efficacy remains uncertain. Additionally, the medication has an unfavorable safety profile.

VIII. As of June 2020, safety data are based on a pooled population in 702 patients, 65% were exposed for six months or greater, and 34% were exposed for over one year. Ninety-five percent of patients received 160 mg twice daily.

IX. Warnings and precautions: hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, impaired wound healing and embryo-fetal toxicity. There are no contraindications. Serious adverse reactions occurred in 33% of patients. The most frequent was pneumonia. Fatal adverse reactions occurred in 3% of individuals due to sepsis (n=1), cardiac arrest (n=3), respiratory failure (N=3).

X. Common adverse reactions (≥25%): increase liver enzymes, laboratory abnormalities (≥25% each, glucose, leukocytes, albumin, calcium, creatinine, alkaline phosphatase, platelets, cholesterol, sodium), dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation. Permanent discontinuation due to adverse reactions occurred in 5%, dose interruptions in 42%, and dose reduction in 31% of patients.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Selpercatinib (Retevmo) has not been sufficiently studied for safety and efficacy for any condition to date.

* 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
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<tr>
<td>Policy created</td>
<td>08/2020</td>
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</table>

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.
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP193

Split Fill Management*

Description
Selumetinib (Koselugo) is a mitogen-activated protein kinase (MEK) inhibitor for both MEK 1 and 2 that inhibits the phosphorylation of extracellular signal related kinase (ERK) and reduces neurofibroma numbers, volume, and proliferation.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>selumetinib</td>
<td>10 mg capsules</td>
<td>Neurofibromatosis type 1 (NF1)</td>
<td>120 capsules/30 days</td>
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<tr>
<td>(Koselugo)</td>
<td>25 mg capsules</td>
<td></td>
<td></td>
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</tbody>
</table>

Initial Evaluation

I. Selumetinib (Koselugo) may be considered medically necessary when the following criteria are met:
   A. Member is between two and 18 years of age; \textbf{AND}
   B. Medication is prescribed by, or in consultation with, a neurosurgeon or neurologist; \textbf{AND}
   C. Documentation of baseline comprehensive ophthalmic assessments; \textbf{AND}
   D. Documentation of baseline assessment of left ventricular ejection fraction (LVEF); \textbf{AND}
   E. Member has NOT experienced disease progression (increase in tumor size or tumor spread) while on a MEK inhibitor [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)]; \textbf{AND}
   F. A diagnosis of \textbf{Neurofibromatosis type 1 (NF1)} when the following are met:
      1. Member has inoperable and symptomatic plexiform neurofibromas (PN); \textbf{AND}
      2. Symptoms affect quality of life (e.g. pain, impaired physical function, compression of vital organs, respiratory impairment, visual dysfunction, and neurological dysfunction); \textbf{AND}
      3. Diagnosis confirmed by genetic testing; \textbf{OR}
         i. Member meets at least one criterion:
            a. Six or more light brown spots (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient; \textbf{OR}
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.

b. Freckling in the axillary or inguinal regions (Crowe sign); OR
c. Optic glioma (OPG); OR
d. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris); OR
e. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis; OR
f. A first-degree relative (parent, sibling, or child) with NF1.

II. Selumetinib (Koselugo) 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 response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; AND
IV. Member has NOT exhibited ophthalmic toxicity (e.g. blurred vision, photophobia, cataracts, or ocular hypertension) nor experienced a decrease of 10% or more below baseline in LVEF during treatment.

Supporting Evidence

I. The safety and efficacy of selumetinib (Koselugo) in pediatric patients two years of age or older with NF1 who have inoperable PN was established in the SPRINT trial (a phase II, open-label, single arm, multicenter clinical trial).
II. Patients older than 18 years of age are being studied in a phase 2, open label, single site clinical trial, with the primary outcome being to determine an objective response rate. The study is still ongoing and therefore has no published safety and efficacy data to support the use in adult patients (those 18 years of age or older).
III. NF1 is a multifaceted disease state and selumetinib (Koselugo) has a complex dosing regimen and safety profile; therefore, it should be prescribed by, or in consultation with, a specialist in the treatment and management of NF1.
IV. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) of 10% or more below baseline, occurred in 23% of the 74 pediatric patients who received selumetinib (Koselugo) in the clinical trial. The safety and efficacy, of use in those with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN, has not been established.
V. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving selumetinib (Koselugo). Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients. Comprehensive ophthalmic assessments...
prior to initiating, and at regular intervals during treatment, for new or worsening visual changes is recommended.

VI. There is no published data from a head-to-head study between selumetinib (Koselugo) and other MEK inhibitors [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)] to show effectiveness for the treatment of pediatric patients two years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

There is no data to show one MEK inhibitor could overcome common mechanisms of resistance of MEK inhibitors.

VII. The safety and efficacy of selumetinib (Koselugo) was evaluated in patients with NF1 who have inoperable (defined as a PN that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN) and symptomatic [defined as PNs that may located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, respiratory impairment, visual dysfunction, and neurological dysfunction] PNs.

VIII. Per the American Academy of Pediatrics, National Institutes of Health (NIH) consensus development conference regarding NF1, to establish a diagnosis of NF1, two out of seven criteria have to have been met: 1. Six or more light brown spots on skin (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient. 2. Two or more neurofibromas of any type or 1 plexiform neurofibroma. 3. Freckling in the axillary or inguinal regions (Crowe sign). 4. Optic glioma (OPG). 5. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris). 6. A distinctive osseous lesion, such as sphenoid wing dysplasia (partial or complete absence of the greater wing of the sphenoid) or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis (unsuccessful spinal fusion). 7. A first-degree relative (parent, sibling, or child) with NF1

A. NF1 genetic testing may be performed for purposes of diagnosis, but if a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. Molecular diagnosis of NF1 is available based on DNA analysis for a pathogenic variant in the NF1 gene. Only 4 genotype-phenotype correlations have been established (deletion of the entire NF1 gene, specific 3-base deletion in exon 22, Amino acid substitution at codon 1809, some missense or splicing variants are associated with “spinal NF1,”).

Investigational or Not Medically Necessary Uses

I. Selumetinib (Koselugo) has not been FDA-approved, or sufficiently studied for safety and efficacy for other conditions except neurofibromatosis type 1 (NF1) with inoperable PNs.
* 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

4. National Cancer Institute (NCI). MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas. ClinicalTrials.gov NCT02407405

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>08/2020</td>
</tr>
</tbody>
</table>
Short-acting Granulocyte-colony stimulating factor (CSF) and Granulocyte macrophage-CSF

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP031

**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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen (filgrastim)</td>
<td>• Bone marrow transplant &lt;br&gt; • Peripheral progenitor cell (PBPC) mobilization and transplant</td>
<td>300 mcg/mL vial &lt;br&gt; 300 mcg/0.5mL syringe &lt;br&gt; 480 mcg/1.6mL vial &lt;br&gt; 480 mcg/0.8mL syringe</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
<tr>
<td>Zarxio (filgrastim-sndz)*</td>
<td>• Prophylactic use in patients with non-myeloid malignancy &lt;br&gt; • Treatment of chemotherapy-induced febrile neutropenia &lt;br&gt; • Neutropenic complications from prior cycle &lt;br&gt; • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy</td>
<td>300 mcg/0.5mL syringe &lt;br&gt; 480 mcg/0.8mL syringe</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
<tr>
<td>Nivestym (filgrastim-aafi)</td>
<td>• Neutropenic complications from prior cycle &lt;br&gt; • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy</td>
<td>300 mcg/mL vial &lt;br&gt; 300 mcg/0.5mL syringe &lt;br&gt; 480 mcg/1.6mL vial &lt;br&gt; 480 mcg/0.8mL syringe</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
<tr>
<td>Granix (tbo-filgrastim)</td>
<td>• Bone marrow transplantation failure or engraftment delay &lt;br&gt; • Severe chronic neutropenia &lt;br&gt; • Myelodysplastic syndrome &lt;br&gt; • Exposure to myelosuppressive doses of radiation</td>
<td>300 mcg/mL vial &lt;br&gt; 300 mcg/0.5mL syringe &lt;br&gt; 480 mcg/1.6mL vial &lt;br&gt; 480 mcg/0.8mL syringe</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
<tr>
<td>Leukine (sargramostim)</td>
<td>• Bone marrow transplantation failure or engraftment delay &lt;br&gt; • Severe chronic neutropenia &lt;br&gt; • Myelodysplastic syndrome &lt;br&gt; • Exposure to myelosuppressive doses of radiation</td>
<td>250 mcg vial</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
<tr>
<td>Releuko (filgrastim-ayow)</td>
<td>• Bone marrow transplantation failure or engraftment delay &lt;br&gt; • Severe chronic neutropenia &lt;br&gt; • Myelodysplastic syndrome &lt;br&gt; • Exposure to myelosuppressive doses of radiation</td>
<td>300 mcg/mL vial &lt;br&gt; 300 mcg/0.5mL syringe &lt;br&gt; 480 mcg/1.6mL vial &lt;br&gt; 480 mcg/0.8mL syringe</td>
<td>15 prefilled syringes or vials per 30-day supply</td>
</tr>
</tbody>
</table>
Initial Evaluation

I. Products may be considered medically necessary when the following criteria below are met:

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

A. A diagnosis of:
1. Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR
2. Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR
3. Bone Marrow Transplant (BMT); OR
4. Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR
5. Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR
6. Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR
7. Prophylactic use in patients with non-myeloid malignancy; AND
   i. Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; OR
   ii. Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater AND one or more of the following co-morbidities:
      a. Elderly patients (age 65 or older) receiving full dose intensity chemotherapy
      b. History of recurrent febrile neutropenia from chemotherapy
      c. Extensive prior exposure to chemotherapy
      d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
      e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor
      f. Patient has a condition that can potentially increase the risk of serious infection (i.e. HIV/AIDS)
      g. Infection/open wounds
      h. Recent surgery
      i. Poor performance status
      j. Poor renal function (creatinine clearance <50)
      k. Liver dysfunction (elevated bilirubin >2.0)
      l. Chronic immunosuppression in the post-transplant setting including organ transplant; OR
8. Myelodysplastic Syndrome; AND
   i. Endogenous serum erythropoietin level of ≤500 mUnits/mL; AND

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.

Washington State Rx Services is administered by

September 01, 2022
ii. Patient has lower risk disease (i.e., defined as IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]); AND

iii. Used for treatment of symptomatic anemia in patients without del(5q); AND

iv. Patient is receiving concurrent therapy with Erythropoiesis Stimulating Agents (ESAs); AND

   a. Patient has ring sideroblasts < 15% and will use in combination with lenalidomide following no response (despite adequate iron stores) or loss or response to an ESA alone; OR

   b. Patient has ring sideroblasts ≥ 15%; OR

9. Treatment of chemotherapy-induced febrile neutropenia; AND

   i. Patient has been on prophylactic therapy with filgrastim; OR

   ii. Patient has not received prophylactic therapy with a granulocyte colony stimulating factor; AND

      a. Patient has one or more of the following risk factors for developing infection-related complications:

         i. Sepsis Syndrome

         ii. Age >65

         iii. Absolute neutrophil count [ANC] <100/mcL

         iv. Duration of neutropenia expected to be greater than 10 days

         v. Pneumonia or other clinically documented infections

         vi. Invasive fungal infection

         vii. Hospitalization at the time of fever

         viii. Prior episode of febrile neutropenia; OR

10. Severe chronic neutropenia; AND

   i. Patient must have an absolute neutrophil count (ANC) < 500/mm3; AND

   ii. Patient must have a diagnosis of one of the following:

      a. Congenital neutropenia

      b. Cyclic neutropenia

      c. Idiopathic neutropenia; OR

11. Management of CAR-T related Toxicity; AND

   i. Patient has been receiving therapy with CAR T-cell therapy (e.g. tisangeneceleuleucel (Kymriah), Axicabtagene Ciloleucel (Yescarta), etc.); AND

   ii. Patient is experiencing neutropenia related to their therapy.

Renewal Evaluation

I. Renewal criteria

   A. Same as initial prior authorization policy criteria
Supporting Evidence

I. All indications listed follow FDA labeled indications or compendia indications

II. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Myeloid Growth Factors Clinical Practice Guideline at NCCN.org.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Added Releuko (filgrastim-ayow) to policy in the non-preferred position</td>
<td>04/2022</td>
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<tr>
<td>Updated quantity level limit to allow 15 doses per 30-day supply</td>
<td>12/2019</td>
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<tr>
<td>Policy title change, designate Zarxio as a preferred product, add “No PA Required” to Initial Evaluation Section 1 boxed information</td>
<td>10/2019</td>
</tr>
<tr>
<td>Previous Reviews</td>
<td>12/2018</td>
</tr>
<tr>
<td>Added Nivestym, biosimilar to Neupogen</td>
<td>10/2018</td>
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<tr>
<td>Previous Reviews</td>
<td>02/2018; 07/2018</td>
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<td>Criteria update. Zarxio is the preferred short-acting G-CSF</td>
<td>2/2017</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP020

Description
Sildenafil (Revatio®), and tadalafil (Adcirca®, Alyq®, Cialis®) are phosphodiesterase type 5 (PDE5) inhibitors.

Length of Authorization
- Initial: Length of benefit
- Renewal: Not applicable

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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</thead>
<tbody>
<tr>
<td>sildenafil (Revatio)</td>
<td>20 mg tablets</td>
<td>Raynaud’s phenomena</td>
<td>90 tablets/30 days</td>
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<tr>
<td></td>
<td>10 mg/mL</td>
<td>Pulmonary arterial hypertension</td>
<td>224 mL/30 days (2 bottles)</td>
<td>185438, 185439</td>
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<tr>
<td>tadalafil (Cialis)</td>
<td>2.5 mg tablets</td>
<td>Benign prostatic hyperplasia</td>
<td>30 tablets/30 days</td>
<td>133138, 133126</td>
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<td></td>
<td>5 mg tablets</td>
<td></td>
<td></td>
<td>085041, 085008</td>
</tr>
<tr>
<td></td>
<td>20 mg tablets</td>
<td>Pulmonary arterial hypertension</td>
<td>60 tablets/30 days</td>
<td>095039, 083319</td>
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<tr>
<td>tadalafil (Adcirca)</td>
<td>20 mg tablets</td>
<td>Pulmonary arterial hypertension</td>
<td>60 tablets/30 days</td>
<td>144282, 143348</td>
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<tr>
<td>tadalafil (Alyq)</td>
<td>20 mg tablets</td>
<td>Pulmonary arterial hypertension</td>
<td>60 tablets/30 days</td>
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</table>

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**

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.
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 Revatio oral suspension 10 mg/mL, and the generic 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 atrial 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.


### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>April 2015</th>
</tr>
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<tr>
<td>Date Effective</td>
<td>April 2015</td>
</tr>
<tr>
<td>Last Updated</td>
<td>May 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>06/15, 03/18, 05/19</td>
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### Action and Summary of Changes

<table>
<thead>
<tr>
<th>Action Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>05/2019</td>
</tr>
<tr>
<td>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.</td>
<td>03/2018</td>
</tr>
</tbody>
</table>

*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.*
simvastatin (Zocor®) 80 mg
UMP POLICY

Policy Type: PA
Pharmacy Coverage Policy: UMP106

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

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin (Zocor)</td>
<td>80 mg tablets</td>
<td>Prevention of cardiovascular events/cardiovascular disease and reduce the risk of atherosclerotic cardiovascular disease, homozygous familial hypercholesterolemia</td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>

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

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

Supporting Evidence
I. In 2011, the FDA issued a dose limitation on simvastatin 80 mg stating that it should not be started in new patients and should only be used in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Furthermore, 2018 AHA/ACC guidelines note simvastatin 80 mg/day is not recommended due to increased risk of myopathy. If patient is unable to achieve LDL-C goal with simvastatin 40 mg/day, switch to a high-intensity statin.
II. The SEARCH trial was a seven-year, randomized, double-blind study that compared the efficacy and safety of simvastatin 80 mg versus simvastatin 20 mg, with or without vitamin B12 and folate in survivors of myocardial infarction.
   - Incidence of major vascular events between the simvastatin 80 mg group and simvastatin 20 mg group was 24.5% vs 25.7%, respectively (95% CI 0.88, 1.01, p=0.10).
   - 0.9% of patients in the simvastatin 80 mg group experienced myopathy versus 0.02% in the simvastatin 20 mg group. Risk for myopathy and rhabdomyolysis was highest in the first 12 months of therapy.

References

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updates to wording of initial criteria in efforts to clarify policy intent</td>
<td>05/2021</td>
</tr>
<tr>
<td>Criteria transitioned to policy with supporting evidence section added.</td>
<td>10/2019</td>
</tr>
<tr>
<td>New criteria</td>
<td>01/2017</td>
</tr>
</tbody>
</table>
sirolimus (Hyftor™)
UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP259

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

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

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

Initial Evaluation

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

II. Sirolimus (Hyftor) is considered investigational when used for all other conditions, including but not limited to:
   A. Tufted angiomas
   B. Fibroma or angiofibroma not associated with tuberous sclerosis complex
   C. Non FDA-approved dermatologic conditions

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.

September 01, 2022
Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND

III. Documentation that member has exhibited improvement or stability in extent and/or severity of angiofibroma (e.g., reduction in angiofibroma size and redness).

Supporting Evidence

I. Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder associated with the formation of benign tumors in various organ systems throughout the body, most commonly including the skin, brain, eyes, heart, kidneys, and lungs. Skin manifestations of TSC occur in up to 95% of individuals and include facial angiofibromas, hypomelanotic macules, fibrous plaques, Shagreen patches, and ungual fibromas. Most patients with TSC present with angiofibromas with onset commonly occurring in early childhood or early adulthood. Angiofibromas are benign reddish pink bumps located on the face, and without treatment they can cause facial disfigurement, bleeding, itching, erythema, and significant psychosocial consequences.

II. Per the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations, the diagnosis of tuberous sclerosis should be confirmed by genetic testing through identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue. In the absence of TSC mutations, diagnosis can be made through identification of clinical features including but not limited to fibrous cephalic plaque, hypomelanotic macules, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma’s, cardiac rhabdomyoma, lymphangiolelomyomatosis, and angiomyolipomas.

III. While there are limited treatment options for this condition, the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations recommend the use of topical compounded sirolimus (category 1 recommendation, based on a high-level of evidence and uniform consensus). Studies have evaluated compounded formulations ranging from 0.1% to 1% in a variety of vehicles. Smaller and flatter appearing lesions tend to respond better to topical sirolimus, so early treatment is recommended.

Sirolimus (Hyftor) has not been evaluated against compounded sirolimus for the treatment of TSC angiofibroma, therefore comparative efficacy and safety remain uncertain. However, the chemical entity in both products is the same, therefore they are expected to provide similar safety and efficacy, even in the absence of a commercially available, FDA-labeled indication for compounded sirolimus. Further, given the long-established safety, efficacy, and cost effectiveness of compounded sirolimus, trial is required prior to use of sirolimus (Hyftor).

IV. Guidelines recommend surgical approaches (category 2B, based on lower-level evidence and consensus that the intervention is appropriate) for angiofibromas rapidly changing in size and/or number, causing pain, bleeding, irritation, disfigurement, or impaired function. These procedures include shave excision, cryotherapy, electrodesiccation, radiofrequency ablation,
dermabrasion, and laser therapy. They have been standardly used for angiofibroma management, though patients may not be candidates for surgery depending on anesthetic risk, age, active infection, uncontrolled diabetes, pregnancy, etc. Contraindications for laser therapy may include malignant carcinoma, irradiation of neck, epilepsy, exposure of retina, cognitive impairment, and pregnancy. Specifically, younger children may benefit from pulsed-dye laser therapy and adolescence ablative laser therapy to reduce facial erythema.

V. The FDA-approval of sirolimus (Hyftor) was based off a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled trial. The study population included 62 adults and pediatric patients greater than 6 years of age, with a definitive diagnosis of TSC, 3 or more reddish papules of facial angiofibromas (> 2 mm diameter), and a past difficulty with or did not want laser or surgical therapy. The concurrent use of any mTOR inhibitor, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D, adapalene, benzyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid, were prohibited. Population characteristics were as follows: mean age 22 years (range of 6-53 years), 42% of patients had intellectual impairment, 60% had epilepsy, 28% had prior mTOR use (including topical sirolimus), and 32% had prior laser therapy, surgical resection, or liquid nitrogen therapy. The primary endpoint was composite improvement of angiofibroma size and color at week 12, which was met with 5 (17%) improved and 13 (43%) markedly improved in the sirolimus group compared to zero participants in the placebo group, with 84% rated unchanged. The secondary endpoints were response rates for composite, size, color, and plaques, and change in Dermatology Life Quality Index (DLQI) and Children’s DLQI (CDLQI). The response rates for size, color, and plaques were statistically significant while the change from baseline in DLQI and CDLQI was not. The most common adverse events included dry skin (40%), application site irritation (37%), and itching (17%). Overall, this was a well-designed phase 3 clinical trial that showed statistical improvement in composite response rate and individual size, color and plaque response rates, however clinical meaningfulness of these endpoints and measurement tool remain unknown. Applicability to the larger TSC population is limited due to a large proportion of the population having previously been treated with surgery, laser or mTOR inhibitor therapy.

VI. The initial authorization length of three months is supported by clinical study duration of 12 weeks and prescribing information guidance which indicates that if symptoms do not improve by week 12 of treatment, prescriber should reevaluate the need for continuation of the medication.

VII. Quantity limits are based on the maximum daily doses used in pivotal study and as indicated by the FDA, and are expected to be sufficient, even if a large majority of the face is impacted. If symptoms do not improve within 12 weeks of consistent use and excessive quantities are needed, alternative treatment strategies that have the potential to be more efficacious and cost effective should be considered.

References

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.

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

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<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Policy created</td>
<td>07/2022</td>
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</table>
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.

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP186

Description
Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are orally administered metabolites of the neurotransmitter GABA that act as central nervous system depressants with an unknown mechanism of action.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>sodium oxybate (Xyrem)</td>
<td>500 mg/mL</td>
<td>Narcolepsy with cataplexy</td>
<td>540 mL/30 days</td>
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<tr>
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<td></td>
<td>Narcolepsy with excessive daytime sleepiness in patients greater than 7 years of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic hypersomnia in adults</td>
<td></td>
</tr>
<tr>
<td>calcium, magnesium, potassium, sodium oxybates (Xywav)</td>
<td></td>
<td>Narcolepsy with excessive daytime sleepiness in patients greater than 7 years of age</td>
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<tr>
<td></td>
<td></td>
<td>Idiopathic hypersomnia in adults</td>
<td></td>
</tr>
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</table>

Initial Evaluation

I. Sodium oxybate (Xyrem) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; AND
   B. Medication is not used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); AND
   C. Confirmation the member does not have a succinic semialdehyde dehydrogenase deficiency; AND
   D. Provider attestation the member does not have a history of substance abuse; AND
   E. A diagnosis of one of the following:
      1. Narcoplexy with cataplexy; AND
         i. Member is seven years of age or older; AND
         ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; AND
iii. Symptoms have been present for at least three months; **AND**
iv. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **OR**

2. **Narcolepsy with excessive daytime sleepiness; AND**
   i. Member is seven years of age or older; **AND**
   ii. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
   iii. Symptoms have been present for at least three months; **AND**
   iv. For members that are 18 years of age or older, treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
      a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
      b. Solriamfetol (Sunosi); **AND**
   v. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **OR**

3. **Idiopathic hypersomnia; AND**
   i. Member is 18 years of age or older; **AND**
   ii. Provider attestation that hypersomnia is not better explained by medical or neurological disorder, mental disorder, medication use, or substance use disorder; **AND**
   iii. Provider attestation that diagnosis has been confirmed via the following:
      a. Polysomnography; **AND**
      b. Multiple sleep latency test; **AND**
   iv. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
      a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
      b. Methylphenidate, amphetamine salts, or dextroamphetamine

II. **Calcium, magnesium, potassium, sodium oxybates (Xywav)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(E) above have been met; **AND**
   B. The member has an FDA labeled contraindication or intolerance to Xyrem; **OR**
      1. Provider attestation member has tried and can not further reduce dietary salt intake via other means (i.e. salt restricted diet, others); **AND**
      2. The member is sensitive to sodium intake due to at least one of the following:
         i. Heart failure
         ii. Hypertension
         iii. Impaired renal function; **AND**
   C. For the settings of narcolepsy with cataplexy or narcolepsy with excessive daytime sleepiness:
      1. Treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated
III. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are considered investigational when used for all other conditions, including but not limited to:
   A. Fibromyalgia
   B. Insomnia

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 cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake); **AND**
IV. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate)

Supporting Evidence

I. The American Academy of Sleep Medicine does not make recommendations on preferring any agents over one another in the settings of narcolepsy or idiopathic hypersomnia. Guidance on the treatment of narcolepsy recommends modafinil and armodafinil as first-line treatment options, stimulants as second-line options due to their adverse event profile, and sodium oxybate (Xyrem) as a third-line option due to its adverse event profile and requirement for a REMS program. Similarly guidance on the treatment of idiopathic hypersomnia recommends modafinil and armodafinil as first-line treatment, stimulants as second-line, sodium oxybate (Xyrem) as third-line. Guidelines have not been updated to include calcium, magnesium, potassium, sodium oxybates (Xywav) at this time for either indication.
II. These agents are a part of a REMS program which only allows certified prescribers and pharmacies to dispense sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav). Prescribers must screen each patient for a history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression or suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents.
III. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are contraindicated in patients taking sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate), and in patients with a succinic semialdehyde dehydrogenase deficiency. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have serious side effects such as, central nervous system depression, abuse and misuse, respiratory depression and sleep-disordered breathing, depression and suicidality, parasomnias, other psychiatric reactions (e.g. anxiety, hallucinations, psychosis), and elevates salt content (use with caution in patients that have heart failure, hypertension, or renal impairment).
IV. Outside of salt content, there is no clinical difference between sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav). Weighing the safety, efficacy, cost, and clinical experience, sodium oxybate (Xyrem) is the plan’s preferred product over calcium,
magnesium, potassium, sodium oxybates (Xywav). Medical necessity of treating with Xywav over Xyrem is limited to members with comorbidities that place them at increased sensitivity to their daily sodium intake (e.g., heart failure, hypertension, impaired renal function). However, allowance of Xywav does not negate the need for the member to continue reduction of dietary salt intake and is not a means of a convenience option for those unwilling to reduce dietary salt intake.

**Narcolepsy with cataplexy/excessive daytime sleepiness:**

V. Patients included in clinical trials had a history of narcolepsy for three months or greater and had chronic narcolepsy that was ongoing.

VI. For the treatment of narcolepsy with cataplexy, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials with a total of 191 patients. Over 80% of patients in these trials were on stimulants as background therapy. The primary efficacy endpoint was the median change from baseline in cataplexy attacks. The baseline number of cataplexy attacks was 20 and 23 for the placebo group and Xyrem 9g group, respectively. Trial one had a reduction of 16 attacks per week in the 9g treatment group and 4 attacks per week in the placebo group (p=0.0016). Trial two was a randomized withdrawal trial, and the placebo group had 21 attacks within two weeks, while the sodium oxybate (Xyrem) group had zero attacks within two weeks (p<0.001).

VII. For the treatment of narcolepsy with excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled trials with a total of 450 patients. The primary efficacy endpoint for trial three was the change from baseline in the Epworth Sleepiness Scale (EPSS). Sodium oxybate (Xyrem) had a -2 and -5 median change from baseline at week 8 for the 6g and 9g treatment groups, and both groups had statistically greater reductions than the placebo group (p<0.001). The primary efficacy endpoint for trial four was the change from baseline in the Maintenance of Wakefulness Test (MWT). Sodium oxybate (Xyrem) had a mean change from baseline of 0.6 compared to -2.7 for placebo at week 8 (p<0.001).

VIII. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in one double-blind, placebo-controlled, randomized-withdrawal trial with 106 pediatric patients. Patients included in this study were seven to 16 years of age. The primary efficacy endpoints were the change in the frequency of cataplexy attacks and EPSS. The median change from baseline in the number of cataplexy attacks per week was 0.3 for sodium oxybate (Xyrem) compared to 12.7 for placebo (p<0.0001). The median change in the EPSS was zero for sodium oxybate (Xyrem) and three for placebo (p=0.0004).

IX. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231). Solriamfetol (Sunosi) demonstrated a change in MWT of 7.7 minutes from baseline, and a change in EPSS of -3.8 from baseline, at week 12 (p<0.0001) for both endpoints against placebo.

X. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in patients with narcolepsy with cataplexy. Patients were all transitioned to the use of calcium, magnesium,
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.

potassium, sodium oxybates (Xywav) and optimized regardless of prior anti-cataplectic therapy or being naïve to treatment (n=201). Once optimized, efficacy was confirmed in the double blind, randomized withdrawal period (DB RWP) of this trial. During the DB RWP, outcomes showed a statistically significant worsening of cataplexy symptoms in patients on placebo when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm. The safety profile in pediatric patients with Xywav is expected to be similar to that of adult patients treated with Xywav and to that of pediatric patients treated with Xyrem.

XI. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. The efficacy of pitolisant (Wakix) was established in three randomized controlled trials (HARMONY I, I bis, and III), and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with excessive daytime sleepiness. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I.

- In HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
- HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries. The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.

XII. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav) to establish superior safety or efficacy of one product over the other. However, there are substantial cost differences between products despite not having any evidence of improved clinical efficacy or safety.

Idiopathic Hypersomnia:

XIII. While sodium oxybate (Xyrem) does not carry an FDA approved indication for use in idiopathic hypersomnia (IH), the active moiety is the same as calcium, magnesium, potassium, sodium oxybates (Xywav). The chemical entity found in both of these products is expected to produce similar efficacy and safety for the treatment of IH.

XIV. The safety profile of calcium, magnesium, potassium, sodium oxybates (Xywav) and sodium oxybate (Xyrem) in pediatric patients for the treatment of IH has not been established.

XV. Idiopathic hypersomnia (IH) is a sleep disorder that presents as chronic excessive daytime sleepiness (EDS) and difficulty waking up from nighttime sleep or daytime naps. Symptomatic
patients are unable to maintain wakefulness and alertness during major waking episodes of the
day, with sleep occurring unintentionally. Diagnosis of IH is made by objective sleep tests as well
as ruling out other sleep disorders, medical or psychiatric disorders, or use of drugs that may be
causing EDS. Hypersomnia associated with psychiatric disorders (i.e., atypical depression, bipolar
depression, dysthymia, etc.) is a differential diagnosis and commonly overlaps with complaints
of excessive daytime sleepiness and may be mistaken for idiopathic hypersomnia if not ruled
out. In patients where hypersomnia may be better explained by other sleep disorders,
psychiatric disorders, or use of certain medications, use of sodium oxybate (Xyrem) and
calcium, magnesium, potassium, sodium (Xywav) is not considered medically necessary, as
treatment of hypersomnia in this setting is guided by correcting the underlying cause.

XVI. IH is diagnosed through combined evaluation of nocturnal polysomnography and a multiple
sleep latency test (MSLT). Polysomnography can exclude causes of excessive daytime sleepiness
(i.e., subtle forms of obstructive sleep apnea) while shortened mean sleep latency and the
number of sleep-onset rapid eye movement sleep periods (SOREMPs) can distinguish between
narcolepsy and IH.

XVII. Stimulants and alerting agents (i.e., modafinil, armodafinil, methylphenidate, amphetamine
salts) for IH are recommended based on experience with these medications in the setting of
excessive daytime sleepiness (EDS) associated with narcolepsy. FDA approval of stimulants and
alerting agents in related sleep conditions such as narcolepsy, American Academy of Sleep
Medicine clinical guideline recommendations, large body of safety data, and proven effects on
EDS support the use of stimulants and alerting agents in IH. Additionally, the majority of clinical
trial population for calcium, magnesium, potassium, sodium oxybates (Xywav) were on a
stimulant/alerting agent at baseline. Given the known safety profile, extensive clinical use, and
cost-effectiveness of these therapies, a trial of stimulants and alerting agents is required.

XVIII. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was
established in a Phase 3, interventional, double-blind, placebo-controlled, randomized
withdrawal trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates
(Xywav) in adult patients with IH. Participants were a median age of 39 years, 71% female, 81%
white and non-Hispanic or Latino. At baseline 2% of patients were taking Xyrem only, 4% were
taking Xyrem in addition to another stimulant/alerting agent, 54% were taking a
stimulant/alerting agent, and 41% were naïve to therapy. CNS stimulants were allowed to
continue throughout the SDP and DB RWP – this occurred in 57% of patients. Baseline Epworth
Sleepiness Scale ESS scores were 16 in calcium, magnesium, potassium, sodium oxybates
(Xywav) and 17 in the placebo groups. Efficacy was confirmed in the double blind, randomized,
2-week withdrawal period (DB RWP). Primary outcome showed a statistically significant
worsening of median ESS in patients on placebo (Δ 5 to 14 points) when compared to those in
the calcium, magnesium, potassium, sodium oxybates (Xywav) arm (Δ 6.5 to 7 points)
(p<0.0001).

XIX. No new safety signals were seen in calcium, magnesium, potassium, sodium oxybates (Xywav)
for its evaluation for use in IH. The most commonly reported adverse events were nausea (21%),
headache (16%), anxiety (12%), dizziness (12%), insomnia (9%), hyperhidrosis (8%), decreased
appetite (8%), vomiting (7%), and dry mouth (6%). Across all study periods (excluding placebo-
controlled patients during DB RWP) 17 (11%) reported adverse effects that led to withdrawal
from the study (e.g., anxiety, nausea, insomnia, fatigue, feeling abnormal, fall, decreased
appetite, dizziness, parathesis, tremor, parasomnia, confused state, hallucination (visual), and irritability). TEAEs leading to discontinuation that were reported by >1 participant included anxiety (n=4), insomnia (n=3), nausea (n=3), and confusion (n=2).

XX. The calcium, magnesium, potassium, sodium oxybates (Xywav) study population included patients previously treated with stimulant/alerting therapy and allowed patients to continue these agents throughout the study. There is evidence to support concomitant use of stimulants and alerting agents (i.e., methylphenidate, solriamfetol, modafinil, etc.) with calcium, magnesium, potassium, sodium oxybates (Xywav) or sodium oxybate (Xyrem).

Investigational or Not Medically Necessary Uses

I. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fibromyalgia
   B. Insomnia

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added criteria for new indication for idiopathic hypomnia (IH). Removal of idiopathic hypomnia from Investigational or Not Medically Necessary Uses section. Added IH criteria to both Xyrem and Xywav sections for policy. Updates to supporting evidence.</td>
<td>12/2021</td>
</tr>
<tr>
<td>Updated route of approval of Xywav to require trial of Wakix; updated language around trial of Xyrem prior to Xywav to require member has a FDA labeled contraindication or intolerance to Xyrem OR member is sensitive to sodium intake and provider attests dietary salt intake cannot be reduced further. Updates to supporting evidence.</td>
<td>04/2021</td>
</tr>
<tr>
<td>Removed need to trial and fail stimulating prior to use with Xyrem for Narcolepsy with excessive daytime sleepiness</td>
<td>01/2021</td>
</tr>
<tr>
<td>Update to add new to market Xywav with requirement to trial and fail or demonstrate contraindication or intolerance to Xyrem. Updated clinical trial background on Xywav.</td>
<td>10/2020</td>
</tr>
<tr>
<td>Transitioned from criteria to policy. Included information on:</td>
<td>05/2020</td>
</tr>
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</table>

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.
- Requirement to be prescribed by or in consultation with a sleep specialist, psychiatrist, or neurologist
- Confirmation of diagnosis for narcolepsy
- Requirement for chronic narcolepsy defined as three-month history
- Requirement that member has functional impairment for activities of daily living
- Updated requirements for trial and failure to one stimulant, and modafinil or armodafinil, and Sunosi

<table>
<thead>
<tr>
<th>Policy created</th>
<th>02/2012</th>
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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.
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP060

Description
Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI).
Pitolisant (Wakix) is a histamine-3 receptor antagonist/reverse agonist.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>solriamfetol (Sunosi)</td>
<td>75 mg tablets</td>
<td>Excessive sleepiness associated with either OSA or narcolepsy</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>150 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
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<tr>
<td>pitolisant (Wakix)</td>
<td>4.45 mg tablets</td>
<td>Excessive daytime sleepiness associated with narcolepsy or narcolepsy with cataplexy</td>
<td>14 tablets/7 days</td>
</tr>
<tr>
<td></td>
<td>17.8 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Solriamfetol (Sunosi) and pitolisant (Wakix) 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 sleep specialist, psychiatrist, or neurologist; AND
   C. A diagnosis of one of the following:
      1. Excessive daytime sleepiness; AND
         i. Narcolepsy without cataplexy; AND
            a. Treatment with the following has been ineffective, contraindicated, or not tolerated:
               i. Stimulant (e.g., methylphenidate, amphetamine, etc.); AND
               ii. Modafinil or armodafinil; AND
               iii. If the request is for pitolisant (Wakix): Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated; OR
         ii. Obstructive sleep apnea (OSA); AND
            a. The request is for solriamfetol (Sunosi); AND
b. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); **AND**
c. Treatment with modafinil or armodafinil has been ineffective, contraindicated, or not tolerated

2. **Narcolepsy with cataplexy; AND**
   i. The request is for pitolisant (Wakix); **AND**
   ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
   iii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving).

**II. Solriamfetol (Sunosi) and pitolisant (Wakix) are considered investigational when used for all other conditions, including but not limited to:**

1. Excessive sleepiness associated with Parkinson’s Disease or glioblastoma
2. Shift work sleep disorder (SWSD)
3. Attention-deficit/hyperactivity disorder (ADHD)
4. Fatigue not related to narcolepsy or OSA
   A. **Solriamfetol (Sunosi)**
      1. Major depressive disorder
      2. Steinert myotonic dystrophy syndrome
   B. **Pitolisant (Wakix)**
      1. Excessive daytime sleepiness associated with obstructive sleep apnea

**Renewal Evaluation**

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake]

**Supporting Evidence**

I. **Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.**

II. **The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231).**
III. In clinical trials, patients with OSA were required to be stable for greater than one month on primary OSA therapy (e.g. CPAP, mandibular advancement device, or surgical intervention) prior to use of solriamfetol (Sunosi).

IV. Stimulants such as amphetamine have not been studied in OSA.

V. Current guidelines for patients with excessive sleepiness associated with narcolepsy recommend modafinil or armodafinil as first-line treatment options. Stimulants are recommended as second line therapy.

VI. The current FDA maximum dose for solriamfetol (Sunosi) is 150 mg per day. Although doses of 300 mg were studied, the 300 mg dose was not approved due to tolerability concerns.

VII. Pitolisant (Wakix) is FDA-approved for the treatment of excessive daytime sleepiness in adults with narcolepsy. Pitolisant (Wakix) is the only agent for the treatment of narcolepsy that is not scheduled at this time. Pitolisant (Wakix) was studied in three randomized controlled trials, and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with EDS. HARMONY I and I bis included modafinil as an active comparator to pitolisant (Wakix).

VIII. HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score. The ESS score has been commonly used in standard practice and was originally validated through a study in 1991.

IX. HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.

X. HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries. The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.

XI. HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).

XII. Pitolisant (Wakix) has a noted contraindication for patients with severe hepatic impairment, as well as a warnings and precaution for QTc prolongation. Common side effects were headache, insomnia, irritability, anxiety, and nausea. Less common side effects of musculoskeletal pain, upper respiratory tract infection, heart rate increase, hallucinations, abdominal pain, sleep disturbance, and decreased appetite were also noted.

XIII. There are no direct head-to-head studies comparing pitolisant (Wakix) and solriamfetol (Sunosi) to establish superior safety or efficacy of one product over the other; however, pitolisant (Wakix) is significantly more costly than solriamfetol (Sunosi) despite not having any evidence of improved clinical efficacy or safety.

XIV. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I. Primary outcomes of HARMONY CTP evaluated weekly rate of cataplexy (WRC) while HARMONY I, Daily Rate of Cataplexy (DRC) was...
evaluated as a secondary endpoint to support the use in cataplexy. Secondary outcomes of DRC in HARMONY I showed a significant improvement DRC.

Investigational or Not Medically Necessary Uses

I. Solriamfetol (Sunosi) and pitolisant (Wakix) currently have no evidence supporting efficacy or safety in the following conditions:
   A. Shift work sleep disorder (SWSD)
   B. Attention-deficit/hyperactivity disorder (ADHD)
   C. Fatigue not related to narcolepsy or OSA
   D. Excessive sleepiness associated with Parkinson’s Disease

II. Solriamfetol (Sunosi) has not been studied in the following indications:
   A. Major depressive disorder
   B. Steinert myotonic dystrophy syndrome

III. Pitolisant (Wakix) is currently being studied for use in excessive daytime sleepiness in patients with obstructive sleep apnea, however, there is currently a lack of sufficient safety and efficacy information to support use in this condition.

References

1. SUNOSI (solriamfetol) tablets, for oral use. Prescribing Information. Palo Alto, CA. Jazz

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removed criteria “Use will not be in combination with sodium oxybate (Xyrem) or calcium, magnesium, potassium, sodium oxybates (Xywav)” After going into the different mechanisms of these drugs, clinical trials, and consulting the team, it was decided that these drugs can be used in combination with each other</td>
<td>12/2021</td>
</tr>
<tr>
<td>Updated policy to include new indication for Wakix use in patients with narcolepsy with cataplexy</td>
<td>12/2020</td>
</tr>
</tbody>
</table>

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September 01, 2022
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.</td>
<td>06/2020</td>
</tr>
<tr>
<td>Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.</td>
<td>09/2019</td>
</tr>
<tr>
<td>New policy for solriamfetol (Sunosi).</td>
<td>08/2019</td>
</tr>
</tbody>
</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP153

Split Fill Management*

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

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>sonidegib (Odomzo)</td>
<td>200 mg capsule</td>
<td>Basal cell carcinoma of the skin, locally advanced</td>
<td>30 capsules/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

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

II. Sonidegib (Odomzo) is considered investigational when used for all other conditions, including but **not limited to**:
   A. Metastatic basal cell carcinoma
   B. Acute leukemia
   C. Breast cancer
   D. Medulloblastoma
   E. Multiple myeloma
   F. Myelofibrosis

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September 01, 2022
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G. Prostate cancer  
H. Breast cancer  
I. Ovarian cancer  
J. Graft versus host disease  
K. Pancreatic cancer  
L. Lung cancer  
M. Hepatocellular carcinoma

Renewal Evaluation

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

Supporting Evidence

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

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

Investigational or Not Medically Necessary Uses

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

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

References

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior authorization transitioned to policy. Addition of age edit, clarification and addition of requirements regarding previous therapies and use of sonidegib (Odomzo) monotherapy. Renewal duration increased for six to 12 months.</td>
<td>11/2019</td>
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sotorasib (Lumakras™)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP244

Split Fill Management*

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

Length of Authorization
- N/A

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>sotorasib (Lumakras)</td>
<td>120 mg tablets</td>
<td>Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation</td>
<td>240 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Sotorasib (Lumakras) is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung cancer (NSCLC).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Sotorasib (Lumakras) is the first therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It is also the first orally administered drug in this setting.

II. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.

III. Most patients with NSCLC including KRAS-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.

Washington State Rx Services is administered by moda HEALTH

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.

September 01, 2022
IV. Sotorasib (Lumakras) received FDA-approval as a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy. The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC has given sotorasib (Lumakras) a Category 2A recommendation as a subsequent-line treatment for NSCLC harboring KRAS G12C mutation, after progression on or after conventional chemotherapy and/or immunotherapy.

V. Sotorasib (Lumakras) was evaluated in CodeBreak100, an ongoing Phase 1 / 2, open-label, single-arm trial. Patients (N=126) with KRAS G12C mutated NSCLC, who had disease progression after chemotherapy and/or immunotherapy were included. All patients received sotorasib (Lumakras) 960 mg orally once a day for a median 15.3 months. Although this is an ongoing clinical trial with the goal to assess efficacy of sotorasib (Lumakras) for multiple oncological settings (NSCLC as well as other solid tumors harboring KRAS mutations), the FDA-approval for sotorasib (Lumakras) was based on outcomes from NSCLC cohort.

VI. The primary efficacy outcome for CodeBreak100 trial was Overall Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Sotorasib (Lumakras) showed an ORR of 37.1% (95% CI; 28.6, 46.2), which included 3.2% complete responses (CR) and 33.9% partial responses (PR). Additionally, participants in this cohort showed DoR of 11.1 months (95% CI; 6.9, NE), PFS 6.8 months (95% CI; 5.1, 8.2), and OS 12.5 months (95% CI; 10.0, NE).

VII. Based on the data from CodeBreak100 trial, the quality of the evidence to support efficacy of sotorasib (Lumakras) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.

VIII. The safety of sotorasib (Lumakras) was based on trial participants (n=126) exposed to therapy. The most common adverse events include diarrhea, nausea, fatigue, and aspartate aminotransferase increase. Serious adverse events (grade 3 or higher) occurred in 42.1% patients and included dyspnea, pneumonitis, and elevation of liver enzymes. At this time, patient population and duration of exposure to sotorasib (Lumakras) are limited to clinical trial participants. Thus, real-world safety profile and patient experience with this drug remain undefined. Based on single-arm, open-label clinical trial in small sample population, the overall safety profile of sotorasib (Lumakras) is largely unknown; thus, it is unknown at this time if benefits of this medication outweigh the risks.

IX. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for sotorasib (Lumakras) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, sotorasib (Lumakras) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and data are not available for review.

X. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

XI. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to...
current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) has been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). Efficacy and safety of sotorasib (Lumakras) in comparison with, or in combination with, currently established regimens, has not been studied and remains unknown.

XIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendation from NCCN, continued approval of sotorasib (Lumakras) as a second-line treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials. As of August 2021, a Phase 3 randomized clinical trial (CodeBreak200) to assess efficacy and safety of sotorasib (Lumakras) in comparison with docetaxel, as a subsequent-line treatment for NSCLC, is underway. Additionally, expanded access program via manufacturer, as part of the ongoing clinical studies of sotorasib (Lumakras), remains a practical option and an alternative path to treatment for qualifying patients.

Investigational or Not Medically Necessary Uses

1. Sotorasib (Lumakras) has not been sufficiently studied for safety and efficacy for any condition to date.

*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


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
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<tr>
<td>Policy created</td>
<td>11/2021</td>
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</table>
**Policy Type: PA/SP**

**Pharmacy Coverage Policy: UMP027**

**Description**
AlphaNine SD, BeneFix, Ixinity, Mononine, and Rixubis are standard half-life factor IX products for the treatment and prevention of bleeding in patients with hemophilia B.

**Length of Authorization**
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (prophylaxis); 6 months (on-demand)

**Quantity limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>AlphaNine SD, coagulation factor IX</td>
<td>500, 1000, 1500 IU</td>
<td>Control and prevention of bleeding episodes: Up to 100 IU/kg; Repeat dose after 12 hours as needed for three to five days. Major hemorrhages may require treatment for up to ten days</td>
<td>Control and prevention of bleeding episodes: Up to the number of doses requested every 28 days</td>
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<tr>
<td>(human)</td>
<td></td>
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<tr>
<td>BeneFIX, coagulation factor IX</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td>Control and prevention of bleeding episodes and perioperative management*: Up to 100 IU/dL; Consider repeat dose after 12 to 24 hours as needed for seven to ten days</td>
<td>Control and prevention of bleeding episodes and perioperative management: Up to the number of doses requested every 28 days</td>
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<tr>
<td>(recombinant)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ixinity, coagulation factor IX</td>
<td>250, 500, 1000 IU</td>
<td>Control and prevention of bleeding episodes**: Up to 100 IU/dL, doses every 12 to 24 hours on days two through 14 until healing is achieved</td>
<td>Control and prevention of bleeding episodes: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td>(recombinant)</td>
<td></td>
<td>Perioperative Management**:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor: Up to 80 IU/dL pre- and post-operative; Repeat every 24 hours on days one through five, depending on type of procedure</td>
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<tr>
<td></td>
<td></td>
<td>• Major: Up to 80 IU/dL pre-op; Post-op: Up to 60 IU, dosed every 8 to 24 hours on days one through three, or up to 50 IU/dL dosed every 8 to 24 hours on days four through six, or up to 40 IU/dL dosed every 8 to 24 hours on days seven through 14</td>
<td></td>
</tr>
<tr>
<td>MonoNine, coagulation</td>
<td>500, 1000 IU</td>
<td>Control and prevention of bleeding episodes and perioperative management:</td>
<td>Control and prevention of bleeding episodes and perioperative management:</td>
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<td></td>
</tr>
<tr>
<td>Product Name</td>
<td>Dosage Form</td>
<td>Indication/ FDA Labeled Dosing</td>
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</table>
| factor IX (human)                |                      | • Minor spontaneous hemorrhage prophylaxis: Up to 30 IU/kg for one dose. Repeat in 24 hours if necessary  
|                                  |                      | • Major trauma or surgery: Up to 75 IU/kg, dosed every 18 to 30 hours depending on T½ and measured factor IX levels. Continue for up to ten days depending on nature of insult | Up to the number of doses requested every 28 days |
| Profilnine SD, factor IX complex | 500, 1000, 1500 IU   | **Control and prevention of bleeding episodes**: Up to 50 IU/dL for a single dose. Daily infusions are generally required  
|                                  |                      | **Perioperative Management**: Up to 50 IU/kg every 16 to 24 hours for seven to ten days until healing is achieved. | Control and prevention of bleeding episodes: Up to the number of doses requested every 28 days |
| Rixubis, coagulation factor IX (recombinant) | 250, 500, 1000, 2000, 3000 IU | **Control and prevention of bleeding episodes**: Up to 100 IU/dL every 12 to 24 hours for seven to ten days, until bleeding stops and healing is achieved  
|                                  |                      | **Routine Prophylaxis**:  
|                                  |                      | • < 12 years: Up to 80 IU/kg twice weekly  
|                                  |                      | • ≥ 12 years: Up to 60 IU/kg twice weekly  
|                                  |                      | **Perioperative Management**: Up to 100 IU/dL every 8 to 24 hours for seven to ten days, until bleeding stops and healing is achieved  | Control and prevention of bleeding episodes: Up to the number of doses requested every 28 days  
|                                  |                      | **Routine Prophylaxis**:  
|                                  |                      | • < 12 years: Up to 672 IU/kg every 28 days  
|                                  |                      | • ≥ 12 years: Up to 504 IU/kg every 28 days  
|                                  |                      | **Perioperative Management**: Up to the number of doses requested every 28 days |

‡ Allows for +5% to account for assay and vial availability  
* One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Adult: Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.3 IU/kg; Pediatric (<15 years): Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.4 IU/kg  
δ One IU per kg body weight increases the circulating activity of factor IX by 0.98 IU/dL  
▪ Initial dose: required factor IX units (IU) = body weight (kg) x desired factor IX increase (% of normal IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)  
▪ Maintenance dose: Depends upon the type of bleed or surgery, clinical response, and the severity of the underlying factor IX deficiency  
€ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX(percent) x 1.0 IU/kg  
γ One IU per kilogram body weight increases the circulating activity of factor IX by 0.7 IU/dL for patients < 12 years of age and 0.9 IU/dL for patients ≥ 12 years of age. Initial dose = body wt (kg) x desired factor IX increase (percent of normal or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)  

Initial Evaluation
I. Standard half-life factor IX products may be considered medically necessary when the following criteria below are met:

   A. Member has a confirmed diagnosis of hemophilia B (congenital factor IX deficiency) the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; AND
      2. Use of standard half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes AND the number of factor IX units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; OR
         ii. Perioperative management of bleeding; OR
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia B (defined as factor IX level of <1%); OR
            b. Member has had more than one documented episode of spontaneous bleeding; AND
      3. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; AND
      4. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Standard half-life factor IX products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For on-demand treatment and routine prophylaxis:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; AND
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; AND
   iii. For on-demand treatment only, the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence
I. Hemophilia B (factor IX deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia B.

II. There are varying severities of hemophilia B depending on the level of factor produced by the patient. Hemophilia B is divided into the following categories based on severity:
   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

III. There are three general approaches to bleeding management in those with hemophilia B:
   - Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia B is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor IX products are the treatment of choice for hemophilia B as recommended by The National Hemophilia Foundation’s Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia B. Therapy should be initiated early with the goal of keeping the trough factor IX level above 1% between doses.

IV. 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.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

**Investigational or Not Medically Necessary Uses**

There is no evidence to support the use of standard half-life factor IX products in any other condition.

**References**

5. Rixubis [package insert]. Westlake Village, CA; Baxalta US Inc.; May 2018

Policy Implementation/Update:

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<th>August 2019</th>
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<td>Date Effective</td>
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<tr>
<td>Last Updated</td>
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<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>New policy created for standard half-life factor products</td>
<td>08/2019</td>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP023

Description
Advate, Afstyla, Hemofil M, Kogenate FS, Koate DVI, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha are standard half-life factor VIII products for the treatment and prevention of bleeding in patients with hemophilia A.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit†</th>
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</thead>
<tbody>
<tr>
<td><strong>Advate</strong>, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 1500, 2000, 3000, 4000 IU</td>
<td>On-demand Treatment: Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine Prophylaxis:</td>
<td>Routine Prophylaxis: Up to 672 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Up to 40 IU/kg every other day (3 to 4 times weekly) or every third day</td>
<td></td>
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<tr>
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<td></td>
<td>Perioperative Management:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat every 12 to 24 hours as needed until bleeding is resolved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Major (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 60 IU/kg preoperative to achieve 100% activity; Repeat every 8 to 24 (every 6 to 24 hours for patients under the age of six) hours to keep factor VIII activity in desired range until healing is complete</td>
<td></td>
</tr>
<tr>
<td><strong>Afstyla</strong>, antihemophilic factor</td>
<td>250, 500, 1000, 1500,</td>
<td>On-demand Treatment: Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
</tr>
</tbody>
</table>

† 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.
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<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit&lt;sup&gt;1&lt;/sup&gt;</th>
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</table>
| (recombinant), single chain                      | 2000, 2500, 3000 IU | Routine Prophylaxis:  
• ≥12 years: Up to 50 IU/kg two to three times per week  
• <12 years: Up to 50 IU/kg two to three times per week. More frequent or higher dosing may be required to account for the higher clearance in this age group.  
Perioperative Management:  
• Minor (e.g. tooth extraction): Up to 50 IU/kg every 8 to 24 hours for at least one day until adequate wound healing, then continue therapy for at least another seven days  
• Major (e.g. intracranial, intrathoracic, or joint replacement): Up to 50 IU/kg every 8 to 24 hours until healing is resolved | Routine Prophylaxis:  
• ≥12 years: Up to 630 IU/kg every 28 days  
• <12 years: Up to 630 IU/kg every 28 days  
Perioperative Management: Up to the number of doses requested for 28 days |
| Hemofil M, antihemophilic factor (human)         | 250, 500, 1000, 1700 IU | On-demand Treatment<sup>5</sup>: Up to 100 IU/dL; Repeat every 8 to 24 hours until the bleeding threat is resolved  
Perioperative Management<sup>4</sup>:  
• Minor (e.g. tooth extraction): A single infusion of up to 80 IU/dL plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases  
• Major (e.g. intracranial, intrathoracic, or joint replacement): Up to 100 IU/dL pre- and post-operative; Repeat dose every 8 to 24 hours depending on state of healing | On-demand Treatment: Up to the number of doses requested every 28 days  
Perioperative Management: Up to the number of doses requested for 28 days |
| Koate DVI, antihemophilic factor (human)         | 250, 500, 1000 IU | On-demand Treatment<sup>5</sup>: Up to 100 IU/dL every 8 to 12 hours until bleeding threat is resolved | On-demand Treatment: Up to the number of doses requested every 28 days |

<sup>1</sup> 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.
<table>
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<th>Indication/ FDA Labeled Dosing</th>
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</thead>
<tbody>
<tr>
<td><strong>Kogenate FS</strong>, antihemophilic factor (recombinant), formulated with sucrose</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td><strong>Perioperative Management</strong>: For major surgical procedures, the factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. Repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of factor replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate homeostasis.</td>
<td><strong>Perioperative Management</strong>: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td><strong>Kovaltry</strong>, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td><strong>On-demand Treatment</strong>: Up to 50 IU/kg every 8 to 12 hours until bleeding is resolved <strong>Routine Prophylaxis</strong>: - Adults: Up to 25 IU/kg three times per week - Children: Up to 25 IU/kg every other day <strong>Perioperative Management</strong>: - <em>Minor</em> (e.g. tooth extraction): Up to 30 IU/kg every 12 to 24 hours until bleeding is resolved - <em>Major</em> (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 50 IU/kg preoperative to achieve 100% activity; Repeat every 6 to 12 hours to keep factor VIII activity in desired range until healing is complete</td>
<td><strong>On-demand Treatment</strong>: Up to the number of doses requested every 28 days <strong>Routine Prophylaxis</strong>: - Adults: Up to 315 IU/kg every 28 days - Children: Up to 368 IU/kg every 28 days <strong>Perioperative Management</strong>: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td>Product Name</td>
<td>Dosage Form</td>
<td>Indication/ FDA Labeled Dosing</td>
<td>Quantity Limit$^1$</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>-------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Novoeight, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>On-demand Treatment</strong>: Up to 100 IU/dL every 8 to 24 hours until resolution of bleed (approximately seven to ten days)</td>
<td><strong>On-demand Treatment</strong>: Up to the number of doses requested every 28 days</td>
</tr>
</tbody>
</table>
| | | **Routine Prophylaxis**:  
• ≥12 years: Up to 50 IU/kg three times per week or up to 40 IU/kg every other day  
• ≤12 years: Up to 60 IU/kg three times weekly or up to 50 IU/kg every other day | **Routine Prophylaxis**:  
• ≥12 years: Up to 630 IU/kg every 28 days  
• ≤12 years: Up to 756 IU/kg every 28 days |
| | | **Perioperative Management**:  
• *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 12 to 24 hours until bleeding is resolved  
• *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL) | **Perioperative Management**: Up to the number of doses requested for 28 days |

$^1$ 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.

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.

September 01, 2022
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| Nuwiq, antihemophilic factor (recombinant) | 250, 500, 1000, 1500, 2000, 2500, 3000, 4000 IU | **On-demand Treatment**: Up to 100 IU/dL every 8 to 24 hours until bleeding risk is resolved  
**Routine Prophylaxis**:  
- ≥12 years: Up to 40 IU/kg every other day  
- ≤12 years: Up to 50 IU/kg every other day or three times per week  
**Perioperative Management**:  
- *Minor* (e.g. tooth extraction): Up to 40 IU/dL every 12 to 24 hours until bleeding is resolved  
- *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours depending on state of healing, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL) | **On-demand Treatment**: Up to the number of doses requested every 28 days  
**Routine Prophylaxis**:  
- ≥12 years: Up to 588 IU/kg every 28 days  
- ≤12 years: Up to 735 IU/kg every 28 days  
**Perioperative Management**: Up to the number of doses requested for 28 days |
| Recombinate, antihemophilic factor (recombinant) | 250, 500, 1000, 1500, 2000 IU | **On-demand Treatment**: Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved  
**Perioperative Management**:  
- *Minor* (e.g. tooth extraction): Up to 80 IU/dL as a single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases  
- *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours depending on state of healing  
**On-demand Treatment**: Up to the number of doses requested every 28 days  
**Perioperative Management**: Up to the number of doses requested for 28 days |
| Xyntha, antihemophilic | 250, 500, 1000, 2000 IU | **On-demand Treatment**: Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved | **On-demand Treatment**: Up to the number of doses requested every 28 days |
## Initial Evaluation

I. Standard half-life factor VIII products may be considered medically necessary when the following criteria below are met:

   A. Member has a confirmed diagnosis of **hemophilia A (congenital factor VIII deficiency)** and the following are met:

      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of standard half-life factor VIII is planned for one of the following indications:
         a. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         b. Perioperative management of bleeding; **OR**
         c. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. Documentation that inhibitor testing has been performed within the last 12 months **AND** if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**


### Table:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
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<tr>
<td>factor (recombinant)</td>
<td></td>
<td>Perioperative Management‡:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minor (e.g. tooth extraction): Up to 60 IU/dL for 3 to 4 days or until adequate hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Major (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
<td></td>
</tr>
</tbody>
</table>

‡ Allows for +5% to account for assay and vial availability
δ Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL); Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg)
4. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval.

II. Standard half-life factor VIII products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For on-demand treatment and routine prophylaxis:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; AND
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; AND
   iii. For on-demand treatment only, the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:
   i. Severe: <1% factor activity (<0.01 IU/mL)
   ii. Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

III. There are three general approaches to bleeding management in those with hemophilia A:
   • Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
   • Perioperative management of bleeding for those undergoing elective surgery/procedures
   • Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation’s Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.
IV. 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.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trials. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of standard half-life factor VIII products in any other condition.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</thead>
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<tr>
<td>Added 1500 strength of Nuwiq</td>
<td>02/2021</td>
</tr>
<tr>
<td>New policy created for standard half-life factor products</td>
<td>08/2019</td>
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</tbody>
</table>
stiripentol (Diacomit®)
UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP318

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

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tr>
<td>stiripentol (Diacomit)</td>
<td>250 mg capsules</td>
<td>Dravet syndrome</td>
<td>180 capsules/30 days</td>
<td>179386</td>
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<td></td>
<td>500 mg capsules</td>
<td></td>
<td>180 capsules/30 days</td>
<td>179387</td>
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<tr>
<td></td>
<td>250 mg powder for oral suspension</td>
<td></td>
<td>180 packets/30 days</td>
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<tr>
<td></td>
<td>500 mg powder for oral suspension</td>
<td></td>
<td>180 packets/30 days</td>
<td>179390</td>
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</table>

Initial Evaluation

I. Stiripentol (Diacomit) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with a neurologist; **AND**
   B. A diagnosis of **Dravet Syndrome** when the following are met:
      i. History of use of clobazam (Onfi); **AND**
      ii. History of use of valproate (Depakote) unless documentation of contraindication or intolerance; **AND**
      iii. Use in combination with clobazam (Onfi); **AND**
      iv. Use in combination with valproate (Depakote) unless documentation of contraindication or intolerance;

II. Stiripentol (Diacomit) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Other non-FDA approve seizure disorder
   C. Primary Hyperoxaluria
   D. Stiripentol (Diacomit) as monotherapy
   E. Use in combination with cannabidiol (Epidiolex)
Renewal Evaluation

I. Documentation of treatment benefit with use of stiripentol (Diacomit) indicated by reduction in generalized tonic-clonic or clonic seizures; **AND**
II. Ongoing use of clobazam (Onfi) and valproate (Depakote) unless documentation of contraindication or intolerance

Supporting Evidence

I. Stiripentol (Diacomit) was studied in two Phase III, multicenter, randomized, placebo-controlled trials with on-going use of clobazam and valproate and demonstrated lack of disease management on clobazam and valproate without stiripentol (Diacomit).
II. The use of stiripentol (Diacomit) has not been studied as monotherapy or in combination with anticonvulsant regimens that do not contain clobazam and valproate.

Investigational or Not Medically Necessary Uses

I. Epileptic encephalopathies associated with SCN1A mutations
   A. Ongoing clinical trials in this setting
II. Other non-FDA approve seizure disorder
   A. Ongoing clinical trials in this setting
III. Primary Hyperoxaluria
   A. Ongoing clinical trials in this setting
IV. Stiripentol (Diacomit) as monotherapy
   A. Stiripentol (Diacomit) has not been studied as monotherapy in Dravet syndrome. Package label also notes lack of clinical data to support the use as monotherapy
V. Use in combination with cannabidiol (Epidiolex)
   A. Stiripentol (Diacomit) has not been studied as combination use with cannabidiol.

References

2. Stiripentol (Diacomit): For Severe Myoclonic Epilepsy in Infancy [Dravet Syndrome] [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Apr. 3, RESULTS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK349320/

Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>February 2019</th>
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<tr>
<td>Date Effective</td>
<td>May 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td></td>
</tr>
<tr>
<td>Last Reviewed</td>
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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.
Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP154

Split Fill Management*

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

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<tbody>
<tr>
<td>sunitinib malate (generic Sutent)</td>
<td>12.5 mg capsule</td>
<td>Gastrointestinal stromal tumor</td>
<td>28 capsules/42 days for all indications except neuroendocrine pancreatic tumor</td>
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<tr>
<td></td>
<td>25 mg capsule</td>
<td>Renal cell carcinoma, adjuvant following nephrectomy</td>
<td>28 capsules/28 days for pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td></td>
<td>37.5 mg capsule</td>
<td>Renal cell carcinoma, advanced</td>
<td>28 capsules/28 days for pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td></td>
<td>50 mg capsule</td>
<td>Neuroendocrine pancreatic tumor</td>
<td></td>
</tr>
<tr>
<td>sunitinib (Sutent)</td>
<td>12.5 mg capsule</td>
<td>Gastrointestinal stromal tumor</td>
<td>28 capsules/42 days for all indications except neuroendocrine pancreatic tumor</td>
</tr>
<tr>
<td></td>
<td>25 mg capsule</td>
<td>Renal cell carcinoma, adjuvant following nephrectomy</td>
<td>28 capsules/28 days for pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td></td>
<td>37.5 mg capsule</td>
<td>Renal cell carcinoma, advanced</td>
<td>28 capsules/28 days for pancreatic neuroendocrine tumor</td>
</tr>
<tr>
<td></td>
<td>50 mg capsule</td>
<td>Neuroendocrine pancreatic tumor</td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

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

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. Treatment with generic imatinib or brand imatinib (Gleevec) has been ineffective, contraindicated, or not tolerated; OR

2. Pancreatic neuroendocrine tumor (pNET); AND
   i. The member has unresectable, locally advanced (stage III), or metastatic (stage IV) disease; OR

3. Renal cell carcinoma (RCC); AND
   i. Disease is advanced (stage III) or metastatic (stage IV)

II. Sunitinib (Sutent) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adjuvant treatment for renal cell carcinoma

III. Sunitinib (Sutent) is considered investigational when used for all other conditions, including but not limited to:
   A. Angiosarcoma
   B. Breast cancer
   C. Colorectal cancer
   D. Central nervous system cancers
   E. Neuroendocrine tumors other than those of pancreatic origin
   F. Gastric cancer
   G. Lung cancer
   H. Soft tissue sarcoma
   I. Thyroid carcinoma
   J. Osteosarcoma
   K. Cholangiocarcinoma
   L. Adenoid cystic carcinoma

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND

III. The request is for generic sunitinib malate; OR
   A. The request is for brand Sutent and treatment with generic sunitinib malate is contraindicated or not tolerated; AND

IV. Sunitinib (Sutent) will be used as monotherapy; AND

V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread
Supporting Evidence

I. Sunitinib (Sutent) was evaluated for gastrointestinal stromal tumor (GIST) in a randomized, double-blind, placebo-controlled trial in adults that had previously progressed on imatinib (Gleevec) or were intolerant to therapy. Outcomes included time-to-tumor progression (TTP), progression-free survival (PFS), and objective response rate (ORR) and were statistically significant in favor of sunitinib (Sutent). At the time of disease progression, treatment was unblinded and those originally on placebo were allowed to crossover to open-label sunitinib (Sutent). At the final analysis overall survival (OS) was not statistically different between the treatment arms.

II. A second study of sunitinib (Sutent) for GIST was conducted as an open-label, single-arm trial in adults that had previously progressed on, or had intolerance to, imatinib (Gleevec). Five of the 55 subjects included had a partial response to therapy (9.1%, CI 3-20%).

III. For renal cell carcinoma (RCC), sunitinib (Sutent) was evaluated in a randomized trial versus IFN-α in treatment-naive RCC. The outcomes evaluated were PFS and ORR, both of which were statistically significant in favor of sunitinib (Sutent).

IV. In the adjuvant treatment setting for RCC, sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial adults with high risk of recurrence following nephrectomy. Subjects were required to have clear cell histology. Subjects were treated for nine cycles maximum. The primary outcome was disease-free survival (DFS) which was statistically significant in favor of sunitinib (Sutent). Overall survival was a secondary endpoint; however, data was not mature at time of analysis and the medication is associated with a significant safety profile.

V. For pancreatic neuroendocrine tumors (pNET), sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial in adults with unresectable disease. The Independent Data Monitoring Committee was terminated early which may have led to an overestimate of the PFS. The outcomes of PFS and ORR were statistically significant in favor of sunitinib (Sutent); however, OS data was not mature at time of analysis. In a follow up analysis at five years a statistical significant different in OS was not demonstrated; however, this may have been confounded by crossover.

VI. Sunitinib has not been evaluated for safety and/or efficacy in pediatric patients. The dosing for sunitinib (Sutent) outside of pancreatic neuroendocrine tumors, is four weeks on two weeks off. A maximum of nine 6-week cycles of therapy for adjuvant RCC has been evaluated and FDA-approved for adjuvant RCC. This is approximately 13 months of therapy total.

Investigational or Not Medically Necessary Uses

I. Adjuvant treatment for renal cell carcinoma

A. Following one year of treatment with sunitinib (Sutent), patients experienced a 1-year improvement in disease free survival compared to placebo; however, there was no improvement in overall survival. Sunitinib (Sutent) is associated with significant toxicity and patients experienced a decline in quality of life while on treatment compared to placebo. NCCN has listed adjuvant sunitinib (Sutent) as a Category 3 recommendation, as there is still no clear role for adjuvant systemic therapy in this setting. Observation or...
II. Sunitinib (Sutent) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:

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

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

References


Policy Implementation/Update:

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<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Addition of trial and failure of generic sunitinib prior to use of branded Sutent. Addition of monotherapy requirements evaluated upon renewal. Updated initial approval duration from three months to six months.</td>
<td>09/2021</td>
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<td>Prior authorization criteria transitioned to policy format. Addition of age edit, monotherapy requirements, and clarification of renal cell carcinoma uses.</td>
<td>11/2019</td>
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<td>Review of adjuvant RCC setting</td>
<td>01/2018</td>
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<td>Policy created</td>
<td>03/2012</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP246

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

Length of Authorization
- Initial:
  i. Upadacitinib (Rinvoq) 45 mg XR tablet: up to two months; maximum two fills per year (one induction treatment per year)
  ii. All other medications: six months
- Renewal:
  i. Upadacitinib (Rinvoq) 45 mg XR tablet: No renewal
  ii. All other medications: 12 months

Quantity Limits

<table>
<thead>
<tr>
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<th>Indication</th>
<th>Dosage Form</th>
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<tr>
<td>abrocitinib (Cibinqo™)</td>
<td>Atopic Dermatitis (AD)</td>
<td>100 mg tablet</td>
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<td></td>
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</tr>
<tr>
<td>baricitinib (Olumiant®)</td>
<td>Rheumatoid Arthritis (RA)</td>
<td>1 mg tablet</td>
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<td>COVID-19ǂ</td>
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<td>upadacitinib (Rinvoq™)</td>
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<td></td>
<td>45 mg XR tablet</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>tofacitinib (Xeljanz®)</td>
<td>Ankylosing spondylitis (AS)</td>
<td>5 mg tablet</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid Arthritis (RA)</td>
<td></td>
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<tr>
<td></td>
<td>Psoriatic Arthritis (PsA)</td>
<td>11 mg XR tablet</td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>
### Polyarticular Juvenile Idiopathic Arthritis (PJIA)

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1mg/mL oral solution (240ml bottle) | Weight-based dosing:  
  - 10 kg-20 kg: 1 bottle/30 days  
  - 20 kg-40 kg: 1 bottle/30 days  
  - Body weight ≥40 kg: 1 bottle/24 days |
| 5 mg tablet     | Body weight ≥40 kg:  
  - 60 tablets/30 days** |

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

** Treatment for alopecia areata falls in the category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes and/or to promote hair growth are excluded from coverage. Please reference the member handbook/certificate of coverage for further information.

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

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

### Ulcerative Colitis (UC)

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg tablet</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td>10 mg tablet</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>11 mg XR tablet</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>22 mg XR tablet</td>
<td>30 tablets/30 days</td>
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</tbody>
</table>

### Applicable to All Disease States and Treatment Options Listed Below

I. Contraindication to one preferred treatment option listed in the policies below does not exempt the requirement to try another required agent prior to biologic approval. For instance, in the rheumatoid arthritis requirements to follow, a contraindication to methotrexate but not to other available treatment options (sulfasalazine, hydroxychloroquine, leflunomide, etc.) would not satisfy criteria I(C)(1). In other words, a member would still need to try at least one of these other agents as clinically appropriate.

II. Approved treatments are not to be used in combination with other biologics or other non-biologic specialty medications used to treat autoimmune conditions. Use of tumor necrosis factor (TNF) blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increased risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of JAK inhibitors with concomitant biologics or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended as there is insufficient data to support their use as dual therapy. Likewise, sufficient data is not currently available to support the safety and efficacy of apremilast use in combination with other agents listed in this policy.

#### Rheumatoid Arthritis

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

   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **rheumatoid arthritis** when the following are met:

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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.

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September 01, 2022
I. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.); **AND**

D. Treatment with one or more tumor necrosis factor (TNF) blockers (e.g., Humira, Enbrel, etc.) has been ineffective, not tolerated, or contraindicated.

II. **Baricitinib (Olumiant)** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(C) above are met; **AND**

B. Treatment with adalimumab (Humira), etanercept (Enbrel), upadacitinib (Rinvoq), AND tofacitinib (Xeljanz/Xeljanz XR) have been ineffective, contraindicated, or not tolerated.

**Renewal Evaluation**

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

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

III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat rheumatoid arthritis or another auto-immune condition (e.g., Humira, Otezla, Remicade, etc.).

**Supporting Evidence**

I. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.

II. The 2021 American College of Rheumatology (ACR) guidelines for rheumatoid arthritis address the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted-synthetic DMARDs (tsDMARDs) such as JAK inhibitors, and biologic DMARDs (bDMARDs) as TNF inhibitors and non-TNF inhibitors. A majority of recommendations are based on low or very low certainty of evidence.

- The 2021 ACR guidelines strongly recommend the use of csDMARD monotherapy (methotrexate preferred) in patients who are DMARD-naive with moderate-to-severe RA. Recommended csDMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Despite moderate evidence in the SELECT-EARLY study noting higher efficacy of upadacitinib over methotrexate in DMARD-naive patients with moderate-to-severe RA, there is limited long-term safety data to strongly recommend the use of tsDMARDs (e.g., JAK inhibitors) as first line therapy. Therefore, methotrexate monotherapy remains the preferred first-line therapy over tsDMARDs in DMARD-naive patients based on established safety and efficacy. Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naive patients.
• For patients who are DMARD-naïve with low disease activity, initial trial of hydroxychloroquine over other csDMARDs, and sulfasalazine over methotrexate is conditionally recommended.

• For DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is conditionally recommended over methotrexate in combination with a TNF inhibitor due to low-certainty evidence with combination use. The recommendation is conditional because patients with poor prognostic factors may benefit from a faster onset of action and greater change of improvement with dual therapy.

• In DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is strongly recommended over the addition of a non-TNF inhibitor or tsDMARD based additional risks of adding a biologic or tsDMARD and low-quality data evaluating superiority over methotrexate monotherapy.

• For patients with moderate-to-severe disease activity despite adequate trial of csDMARD monotherapy, a treat-to-target approach is strongly recommended and the addition of a bDMARD or tsDMARD is conditionally recommended as combination therapy may provide a more rapid treatment response. The recommendation was based on very low certainty of evidence.

• The guidelines conditionally recommend switching to a bDMARD or tsDMARD of a different class over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target, however the recommendation is based on very low-quality evidence supporting greater improvement in disease activity among patients switching therapy classes. There are no current recommendations for using a bDMARD over a tsDMARD, however patients and providers should engage in a shared decision-making approach based on the available safety data of JAK inhibitors.

• The 2021 ACR guidelines have additional recommendations for patient specific populations, including patients with co-morbid heart failure, lymphoproliferative disorder, Hepatitis B infection, nonalcoholic fatty liver disease (NAFLD), persistent hypogammaglobulinemia without infection, and populations with history of serious infection(s).

III. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients with highly active RA despite treatment with csDMARDs may receive a bDMARD or JAK inhibitor based on high level of evidence. Biologic DMARDS (TNF-inhibitors, IL-6 inhibitors, etc.) were previously recommended over JAK inhibitors, but newer data comparing JAK inhibitors to adalimumab failed to demonstrate clinically relevant endpoints favoring bDMARDs over JAK inhibitors.

IV. There are currently no head-to-head trials comparing the safety and efficacy of Xeljanz, Rinvoq, or Olumiant in patients with rheumatoid arthritis.

References


Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Tofacitinib (Xeljanz)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of Polyarticular Juvenile Idiopathic Arthritis (PJIA) when the following are met when the following are met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine; **AND**
   D. Treatment with one or more tumor necrosis factor (TNF) blockers (e.g., Humira, Enbrel, etc.) has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

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

Supporting Evidence

I. The above agent is approved for pediatric patients greater than two years of age with polyarticular juvenile idiopathic arthritis that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA...
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III. The 2019 ACR JIA guidelines for non-systemic polyarthritis (PJIA) strongly recommend initial therapy with a DMARD for all patients with JIA and active polyarthritis; methotrexate has the strongest evidence, but sulfasalazine and leflunomide can also be used. Adjunctive therapy with NSAIDs and oral or intra-articular glucocorticoids is common. Regardless of disease activity, initial therapy with a DMARD is recommended over a biologic, though there may be certain situations where a biologic as initial therapy is preferred (i.e., high-risk joints such as cervical spine, wrist, or hip involved). ACR notes that while initial treatment with biologics was studied in the TREAT-JIA and ACUTE-JIA studies, results were not deemed conclusive enough to make recommendations for biologics as initial therapy at this time. For patients with continued moderate to high disease activity, the guidelines recommend adding a TNF inhibitor, abatacept, or tocilizumab as second-line. The ACR guidelines make a conditional recommendation for switching to non-TNF inhibitor biologics (tocilizumab and abatacept) in patients receiving a TNF inhibitor with continued moderate or high disease activity. It is noted that a second TNF inhibitor may be appropriate for patients who had a good initial response to the first TNF inhibitor but had secondary failure due to suspected drug antibodies developing, and that this conditional recommendation stems from data in adult rheumatoid arthritis patients. Juvenile psoriatic arthritis follows the same treatment paradigm.

IV. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients aged 2-17 years old with active PJIA and who had inadequate response to at least one DMARD or biologic DMARD. The primary endpoint evaluated the occurrence of disease flare at week 44 and was found to be statistically significantly lower in tofacitinib (Xeljanz) group vs the placebo group (29.2 % vs 59.2%, p-value=0.0031). The secondary endpoint found improvements from baseline in questionnaires JIA ACR 30/50/70 and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) in tofacitinib vs placebo. Some limitations to the study include potential bias in the open label arm of the study, and the study is unpublished with limited information such as the population of patients currently on DMARD or oral glucocorticoid.

V. Dosing for PJIA is based on body weight. Patients with body weight greater than ≥40kg on the oral solution may be switched to Xeljanz 5 mg tablets.

References

Psoriatic Arthritis

Initial Evaluation

I. Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   C. A diagnosis of active psoriatic arthritis when the following are met:
      1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
      2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
         i. Erosive disease
         ii. Elevated CRP or ESR
         iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)
         iv. Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis) or functionally limiting arthritis at a few sites; **AND**
   D. Treatment with one or more tumor necrosis factor (TNF) blockers (e.g., Humira, Enbrel, etc.) has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

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

Supporting Evidence

I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are approved for adult patients with psoriatic arthritis (PsA) that had an inadequate response or intolerance to tumor necrosis factor (TNF) inhibitors based on safety and efficacy data from randomized-controlled trials.

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II. The 2018 ACR guidelines for psoriatic arthritis make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.

III. A systematic review of RCTs published in 2015 examined differences in terms of ACR20 response with biologic versus synthetic DMARDs. A statistically significant benefit was not demonstrated with methotrexate, cyclosporine, or sulfasalazine. Leflunomide did demonstrate a statistically significant benefit, though the magnitude of benefit was lower than all of the biologic DMARDs analyzed. There are many limitations to this review, such as a large proportion of trials/data that only included a small number of patients (less than 100). A recent study compared the TNF inhibitor etanercept to methotrexate monotherapy in patients naïve to both biologics and methotrexate. Patients treated with etanercept were statistically more likely to achieve ACR20 response at week 24 compared to the methotrexate monotherapy group (difference 9.2%, 95% CI 1.0 to 17.3, p = 0.029).

IV. The 2018 ACR guidelines for psoriatic arthritis also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). As of January 2022, guidelines have not been updated to place upadacitinib in the PsA treatment algorithm.

References

Ankylosing Spondylitis

Initial Evaluation

I. **Tofacitinib (Xeljanz) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of ankylosing spondylitis when the following are met:
1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; AND
2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; AND
3. Disease manifested as axial disease; OR
4. Disease manifested as peripheral arthritis; AND
E. Treatment with one or more tumor necrosis factor (TNF) blockers (e.g., Humira, Enbrel, etc.) has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

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

Supporting Evidence

I. Tofacitinib (Xeljanz) or upadacitinib (Rinvoq) are approved for adult patients with active ankylosing spondylitis (AS or ax-SpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. The 2019 ACR/SAA/SPARTAN guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% responding). Recommendations against the use of non-biologic DMARDs are made for patients with active ankylosing spondylitis despite NSAID treatment. Some benefit has been seen in patients with peripheral arthritis, thus treatment with sulfasalazine or methotrexate may be considered in patients with predominantly peripheral disease; however, evidence is based on older RCTs with very low quality of evidence. For those patients with inadequate response despite continuous NSAID treatment, the ACR strongly recommends use of TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with secukinumab or ixekizumab over sulfasalazine, methotrexate, or tofacitinib. In patients with primary nonresponse, defined as absence of improvement after 3-6 months of treatment initiation, secukinumab or ixekizumab is conditionally recommended over switching to a different TNF inhibitor. In patients with secondary nonresponse to TNF inhibitors, the guidelines conditionally recommend treatment with a different TNF inhibitor over treatment with a non-TNF inhibitor biologic. The guidelines have not been updated with regard to place in therapy for upadacitinib as of June 2022.
III. The 2016 ASAS/EULAR guideline mirrors that of the ACR/SAA/SPARTAN guidelines. NSAIDs are also noted as first-line treatment due to robust response of greater than 70% of patients achieving ASAS20, and greater than 50% of patients achieving ASAS40 response. In order to qualify for treatment with biologics, ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks, have a trial of glucocorticoid injection or sulfasalazine if peripheral symptoms, and have a high disease activity as defined by a BASDAI of at least 4 or an ASDAS of at least 2.1. The guidelines recommend patients that fail TNF inhibitor therapy, switching to another TNF inhibitor or IL-17 inhibitor can be considered. The ASAS/EULAR guidelines have not been updated with regard to tofacitinib or upadacitinib place in therapy. The panel notes there is still some debate as to whether the two diseases (radiographic and non-radiographic) should be considered as two different entities, given that some patients with non-radiographic disease may develop radiographic changes over time (and some may not).

References

2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated May 2022.

Ulcerative Colitis

Initial Evaluation

I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **moderate to severe ulcerative colitis** when the following are met:
      1. Previous treatment with at least one systemic corticosteroid (e.g., budesonide, prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective to induce remission, is contraindicated, or is not tolerated; **AND**
      2. If systemic corticosteroids were used to induce remission, previous treatment with at least one thiopurine (azathioprine or 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated; **AND**
   D. Treatment with one or more tumor necrosis factor (TNF) blockers (e.g., Humira, Remicade, etc.) has been ineffective, not tolerated, or contraindicated.

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September 01, 2022
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; \textbf{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; \textbf{AND}

III. Member has exhibited improvement or stability of disease symptoms; \textbf{AND}

IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ulcerative colitis or another auto-immune condition (e.g., Remicade, Entyvio, Cimzia, etc.)

Supporting Evidence

I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients over eighteen years of age that had an inadequate response or intolerance to one or more TNF inhibitors based on safety and efficacy data from randomized-controlled trials. As of May 2021, only adalimumab (Humira) has been FDA approved in moderate to severe ulcerative colitis in pediatric patients aged 5 years and older.

II. Tofacitinib (Xeljanz), adalimumab (Humira), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), and upadacitinib (Rinvoq) have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), and golimumab (Simponi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.

III. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, overall quality of evidence supporting this...
recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence. As of May 2022, the guidelines have not been updated to include upadacitinib (Rinvoq).

IV. Patients who are primary non-responders to an anti-TNF therapy should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class. In patients with moderate to severe active ulcerative colitis who had an initial response but subsequently lost efficacy to one anti-TNF therapy, clinical guidelines recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.

V. The 2018 European Crohn’s and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical guidelines recommend treatment with oral systemic corticosteroids if patients are in the higher end of the moderate disease range and treatment with thiopurines for maintaining remission in children who are corticosteroid-dependent or relapsing frequently despite 5-ASA treatment, and 5-ASA intolerant patients. The guidelines recommend infliximab (e.g., Remicade, Inflectra) in chronically active or steroid-dependent ulcerative colitis, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission. Adalimumab (Humira) or golimumab (Simponi) could be considered in those who initially respond but then lose response or intolerant to infliximab (e.g., Remicade, Inflectra), based on serum levels and antibodies. Vedolizumab (Entyvio) should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure.

**References**

2. Upadacitinib [Rinvoq] [Prescribing Information]. North Chicago, IL; AbbVie. Updated May 2022.
Atopic Dermatitis

Initial Evaluation

I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria are met:
   
   A. Member is 12 years of age or older; **AND**
   
   B. Medication is prescribed by, or in consultation with, a dermatologist or an allergist; **AND**
   
   C. A diagnosis of **moderate to severe atopic dermatitis** when the following are met:
      
      1. Body surface area (BSA) involvement of at least 10%; **OR**
      
      i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
      
      2. Treatment with at least two of the following groups has been ineffective or not tolerated, or all are contraindicated:
         
         i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
         
         ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
         
         iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**
      
      3. Documentation that a trial of systemic immunosuppressant, including a biologic, was ineffective, not tolerated, or all are contraindicated.

II. **Abrocitinib (Cibinqo)** may be considered medically necessary when the following criteria are met:

   A. Member is 18 years of age or older; **AND**
   
   B. Criteria I(B) - I(C) above are met; **AND**
   
   C. Treatment with upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

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

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

III. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant); **AND**

IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening.
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. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age).

II. Treatment for moderate-to-severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) has been evaluated and is FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.

III. Upadacitinib (Rinvoq) is FDA approved in patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. Due to safety concerns, use of other systemic drugs is recommended prior to use of upadacitinib (Rinvoq).

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

References


Investigational or Not Medically Necessary Uses

I. Combination use with topical and systemic JAK inhibitors
   A. The safety profile of systemic JAK inhibitors is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib is...
unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy (ruxolitinib) has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed.

II. COVID-19 or associated symptoms or complications
   A. The role of JAK-inhibitors in the treatment of COVID-19 is evolving and varies among available guidelines. Long-term data is not available and continuing therapy beyond hospitalization has not been evaluated for safety and efficacy.

III. Various dermatologic conditions (including, but not limited to plaque psoriasis, guttate psoriasis, vitiligo, dermatomyositis, lichen planus)
   A. Case reports suggest that the use of TNF inhibitors may induce flares when used for guttate psoriasis. Typical treatment involves phototherapy and topical corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics, JAK inhibitors, or targeted DMARDs in this setting at this time.
   B. A systematic review by Ciechanowich et al. evaluated the use of JAK inhibitors in psoriasis, atopic dermatitis, and vitiligo. Seventeen studies (11 randomized controlled trials, 4 case reports, 1 retrospective case series, and 1 open-label clinical trial) were included in the review and concluded that there is limited data to suggest the safety and efficacy of JAK inhibitors in various dermatologic diseases.

IV. Alopecia Areata/Alopecia Totalis/Alopecia Universalis
   A. Baricitinib (Olumiant) has FDA approval for alopecia areata; therapies for alopecia are in a category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes and/or to promote hair growth are excluded from coverage. Of note, not all JAK inhibitors have been evaluated or are FDA-approved for this condition.

V. Atopic Dermatitis – Olumiant (baricitinib)
   A. Two phase III, double-blind, multicenter monotherapy trials BREEZE-AD1 and BREEZE-AD2 studies concluded baricitinib 2mg, 4mg reached its primary endpoint of Validated Investigator’s Global Assessment at week 16 compared to placebo. The manufacturer reports a statistical improvement in Investigator’s Global Assessment (IGA) scores at week 16 compared to placebo, baricitinib improved clinical signs and symptoms in patients with moderate-to-severe AD within 16 weeks of treatment and induced rapid reduction of itch. The safety profile remained consistent with prior findings from baricitinib clinical development in AD, with no new safety concerns. The drug remains in clinical development and is considered experimental and investigational at this time. Three clinical trials are currently ongoing which may provide further confirmation of safety and efficacy.

VI. Familial Mediterranean Fever
   A. Current studies for Familial Mediterranean Fever, a subgroup of periodic fever syndrome, are limited to case reports. In evaluating current evidence available, quantitative evaluation of response to biologic treatments (e.g., tocilizumab, infliximab, etanercept, adalimumab, anakinra and canakinumab) is difficult to obtain, and therefore, difficult to assess true efficacy and safety. In the absence of controlled studies to evaluate the safety and efficacy of biologics in the treatment of patients with Familial Mediterranean Fever, the use of biologics in this setting would be considered experimental and investigational.
VII. Lupus Nephritis, Systemic Lupus Erythematosus (SLE), and Cutaneous Lupus Erythematosus (CLE)
   A. In a 24-week phase II RCT evaluated baricitinib in adults with highly active SLE exhibiting skin and joint symptoms despite the standard treatment, 314 patients were randomly assigned to receive placebo, baricitinib 2 mg, or baricitinib 4 mg. At week 24, baricitinib 4 mg dose (p=0.0414), but not the 2 mg dose, improved the signs and symptoms of active SLE. The short follow-up/study design limit the findings from this study.
   B. Lilly and Incyte have decided to end lupus development for Olumiant (baricitinib) after receiving topline efficacy data from two Phase III studies (SLE-BRAVE 1 and SLE-BRAVE 2) in adults with active lupus. While Olumiant (baricitinib) reached the primary endpoint in one trial (SLE-BRAVE 1), follow up trial (SLE-BRAVE 2) failed to meet the primary endpoint and neither trial achieved key secondary endpoints.

References


**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.*

<table>
<thead>
<tr>
<th>Policy</th>
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<tr>
<td>Chronic Inflammatory Disease Policy</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td></td>
<td>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</td>
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<td>Enthesitis-Related Arthritis (ERA)</td>
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<td>Non-radiographic Axial Spondyloarthritis</td>
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<td>Plaque Psoriasis</td>
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<td>Ulcerative Colitis</td>
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<td>Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)</td>
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<td>ruxolitinib (Jakafi®, Opzelura™) Policy</td>
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<td>Polycythemia vera</td>
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<td>Graft-Versus-Host Disease</td>
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<td>Atopic dermatitis</td>
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<td>fedratinib (Inrebic®) Policy</td>
<td>Myelofibrosis</td>
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**Policy Implementation/Update**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>Added new indication for Rinvoq in the setting of active ankylosing spondylitis, updated supportive evidence, and reference section. Added new indication of alopecia areata for baricitinib (Olumiant®) noting this is an excluded indication.</td>
<td>06/2022</td>
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<tr>
<td>Added Rinvoq’s new indication of Ulcerative Colitis, updated supporting evidence section; added new criteria for Rinvoq in the setting of Atopic Dermatitis to require use of systemic immunosuppressants, including biologic agents first to align per label; added Olumiant’s indication of COVID-19 and new tablet strength in the QL table; removed AS from E/I section given recent FDA-approval of Rinvoq in AS; updated formatting.</td>
<td>05/2022</td>
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<tr>
<td>Added Cibinqo for the setting of Atopic Dermatitis, built out the Atopic Dermatitis criteria section in the policy for Cibinqo and Rinvoq with new FDA approvals. Updated PJIA supporting evidence and references to further clarify guidelines and treatment algorithm and align with Chronic Inflammatory Disease policy.</td>
<td>03/2022</td>
</tr>
<tr>
<td>Added new indications for Rinvoq in setting of PsA and Xeljanz in AS. Updated AS supporting evidence and references to include 2019 guideline update. Added criteria for all diagnoses requiring trial of TNF blockers prior to JAK inhibitor therapy as recommended by FDA labeling. Experimental and investigational section updated to include warning on combination of topical and oral JAK inhibitors and alopecia areata. Added new Rinvoq 30mg tablet availability for atopic dermatitis.</td>
<td>02/2022</td>
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<tr>
<td>Created the Janus Associated Kinase Inhibitor policy. Added Rinvoq and Xeljanz to preferred product mix (effective 1/1/2022). Added Related Policies section.</td>
<td>12/2021</td>
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</table>

**Previous policy changes (relevant from Chronic Inflammatory Policy)**

| Updated criteria for ulcerative to modify the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated. | 06/2021 |
| Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data | 11/2020 |
| Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya). | 08/2020 |

Criteria updated to new policy format. Specific changes include:

**Rheumatoid Arthritis**
- Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
- Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint
- Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated
- Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative

**Polyarticular Juvenile Idiopathic Arthritis (PJIA)**
- Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
- Added route to approval of Actemra as Actemra was previously in a separate policy

**Psoriatic Arthritis**
- Added requirement of the presence of active severe disease and provided specific indicators of severe disease
- Added clinical note: “If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria.”

**Ulcerative Colitis**
- Added age of 18 years or older
- Addition of trial of thiopurine for at least 8 weeks

Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist. | 07/2018 |

Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits. | 06/2018 |
New Criteria Set – consolidated from all biologic agents along with Otezla and Xeljanz criteria sets. Within this new criteria set, here are the following updates:

1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis.
2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz
3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz).
4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally.
5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP034

Description
Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are orally administered transthyretin stabilizers.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

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<th>Product Name</th>
<th>Dosage Form</th>
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<td>Cardiomyopathy of wild type or hereditary</td>
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<td>transthyretin-mediated amyloidosis</td>
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<tr>
<td>(Vyndamax)</td>
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Initial Evaluation

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) may be considered medically necessary when the following criteria below are met:
   A. Member 18 years or older; **AND**
   B. Medication is prescribed by or in consultation with a neurologist or cardiologist; **AND**
   C. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)]; **AND**
   D. A diagnosis of **cardiomyopathy of wild type (ATTRwt-CM) or hereditary transthyretin-mediated amyloidosis (hATTR-CM)** when the following are met:
      1. Confirmed transthyretin-mediated amyloidosis by one of the following:
         i. Documented presence of amyloid deposit by biopsy; **OR**
         ii. Presence of transthyretin precursor protein confirmed by scintigraphy (i.e. radiotracer 99m technetium pyrophosphate (99mTc-PYP)) **AND**
      2. History of heart failure; **AND**
      3. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; **AND**
      4. New York Heart Association (NYHA) functional class I-III; **AND**
      5. No prior history of liver or heart transplantation

II. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered **not medically necessary** when used for all other conditions, including but **not limited to**:

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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.*

September 01, 2022
A. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV

III. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered investigational when used for all other conditions, including but not limited to:
   A. Polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTR-PN) or familial amyloid polyneuropathy (FAP)
   B. Primary (light chain) amyloidosis

Renewal Evaluation

I. Member has previously received treatment with tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax); AND
II. Documentation that the patient has experienced a positive clinical response therapy (e.g., reduced cardiovascular hospitalizations, improved quality of life, slowing of disease progression, etc.); AND
III. No prior history of liver or heart transplantation; AND
IV. New York Heart Association (NYHA) functional class I-III; AND
V. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)].

Supporting Evidence

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are transthyretin stabilizers FDA approved for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
II. Vyndamax (tafamidis) was developed for patient convenience. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are not substitutable on a per-mg basis.
III. Tafamidis meglumine (Vyndaqel) was studied in a phase 3, multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (ATTR-ACT trial). The trial met its primary endpoint, demonstrating a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations (p<0.0001) in the pre-specified pooled tafamidis meglumine (Vyndaqel) 20-mg and 80-mg groups versus placebo at 30 months. Tafamidis meglumine (Vyndaqel) also showed a lower rate of decline in distance for the 6-minute walk test and lower rate of decline in the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS). Of note, subgroup analysis of patients identified as NYHA class III at baseline did not show a reduction in all-cause mortality or cardiovascular related hospitalizations. In the NYHA class III patients, cardiovascular related hospitalizations were actually higher among patients receiving tafamidis meglumine (Vyndaqel) than those receiving placebo.
IV. NYHA Classification - The Stages of Heart Failure:
- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain. Comfortable at rest.
- Class IV - Severe limitations. Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

V. Patients included in the pivotal trial had a history of heart failure, evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm, and confirmed transthyretin-mediated amyloidosis by documented presence of amyloid deposit by biopsy and/or presence of transthyretin precursor protein confirmed by scintigraphy.

VI. Nuclear scintigraphy is a newer, less invasive diagnostic method thought to improve the diagnosis rate of ATTR-CM. Though use of this diagnostic tool may be limited, due to the specialized nature of the protocol and the skill needed for interpretation of the results. There are two radiolabeled phosphonates that have been studied most in this setting, $^{99m}$Tc-pyrophosphate ($^{99m}$Tc-PYP) in the US and $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD) in Europe. In the US, the radiotracer $^{99m}$technetium pyrophosphate, or $^{99m}$Tc-PYP, is not FDA-approved for the diagnosis of ATTR-CM, but it is increasingly used by the medical community.

VII. Patients were excluded if they had NYHA Class IV heart failure, primary amyloidosis, or a history of liver or heart transplantation.
- Primary amyloidosis was excluded as this diagnosis is considered emergent and entails a different treatment approach consisting of chemotherapy.
- Before the availability of tafamidis the management of ATTR-CM consisted of symptomatic treatment of heart failure symptoms and liver and/or heart transplantation. Orthotopic liver transplant (OLT) is one of the most established, potentially curative treatment options for some patients with ATTR-CM, specifically patients with early-stage hATTR. Orthotopic heart transplant (OHT), alone or in combination with OLT, may be a therapeutic option for select patients with ATTR-CM.
- Tafamidis meglumine (Vyndaqel) is designed to target the underlying disease process in ATTR-CM through inhibition of the TTR tetramer dissociation. This forms the rationale for the use of tafamidis meglumine to slow disease progression. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

VIII. Tafamidis meglumine (Vyndaqel) was studied as monotherapy. There is no data on the use of combination therapy with other medications indicated for different types of amyloid disease.
IX. Within the pivotal trial results, a greater proportion of patients in the tafamidis meglumine group either improved upon or remained at their respective NYHA baseline classification compared with patients in the placebo group.

Investigational or Not Medically Necessary Uses

I. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV
   A. In the ATTR-ACT trial, patients with NYHA Class IV were excluded from the pivotal trial. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

II. Polyneuropathy of hereditary transthyretin-mediated amyloidosis or familial amyloid polyneuropathy (FAP)
   A. Coelho et al. 2012 reported no significant changes in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP) as coprimary endpoints were not met in the ITT population.
   B. The US FDA did not approve tafamidis meglumine (Vyndaqel) use in FAP during a filing in 2012, due to limited efficacy data. The agency requested the completion of a second efficacy study to establish substantial evidence of effectiveness prior to an approval.

III. Primary (light chain) amyloidosis
   A. In the pivotal trial (ATTR-ACT), patients with primary amyloidosis were excluded. Primary amyloidosis is caused by a bone marrow disorder. Treatment consists of chemotherapy or bone marrow transplant.

References


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<th>May 2019</th>
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Action and Summary of Changes

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Policy Type: PA

Pharmacy Coverage Policy: UMP065

Split Fill Management*

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

Length of Authorization
- Initial: Three months
- Renewal: Twelve months

Quantity limits

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<td>talazoparib (Talzenna)</td>
<td>Breast cancer, locally advanced or metastatic, BRCA-mutated</td>
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*Quantity limit exceptions are limited to dose reductions and clinician review

Initial Evaluation

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

II. Talazoparib (Talzenna) is considered **investigational** when used for all other conditions, including but not limited to:
   A. When used in combination with any other chemotherapy or targeted therapy
B. Early-stage breast cancer  
C. Ovarian cancer, fallopian tube, and peritoneal cancer  
D. Lung cancer  
E. Prostate cancer

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. Talazoparib (Talzenna) 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]); **AND**
IV. Clinical documentation of response to treatment (e.g., stabilization of disease or decrease in tumor size, or tumor spread).

Supporting Evidence

I. Talazoparib (Talzenna) is FDA-approved for the treatment of adults with germline BRCA mutated (gBRCAm), HER2-negative, locally advanced or metastatic disease.
II. The efficacy and safety of talazoparib (Talzenna) monotherapy was demonstrated in an open-label randomized trial (EMBRACA) which enrolled adult patients that had a deleterious or suspected deleterious germline BRCA1/2 mutation detected by testing with BRACAnalysis.
III. Overall, 431 patients were randomized 2:1 to receive talazoparib or chemotherapy of the provider’s choice (capecitabine, eribulin, gemcitabine or vinorelbine); 287 patients received talazoparib and 144, chemotherapy. Baseline characteristics of both groups were generally similar, but the talazoparib included a higher number of patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 1 or 2 and a higher number of patients whose disease progressed to advanced within 12 months of initial diagnosis.
IV. To be included in the EMBRACA study, patients had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane or an anthracycline, or both, unless contraindicated. Additionally, previous neoadjuvant or adjuvant platinum-based therapy was allowed, provided the patient had a disease-free interval for at least six months after the last dose. Patients were excluded if they had disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., progression of disease within approximately eight weeks after the last dose). Third, patients included in the study had no more than three prior therapies in the advanced breast cancer setting. More than two therapies in other settings (e.g. neoadjuvant, adjuvant) do not apply. However, as current guidelines move to testing for targeted therapies once diagnosed, the likelihood of patients using over one line of therapy is rare.
V. The primary endpoint of the study was radiologic progression-free survival (PFS) done via imaging at baseline, every 6 weeks until week 30, and then every 9 weeks after. The median
progression-free survival was significantly longer among patients in the talazoparib group than among patients in the standard-therapy group (8.6 months [95% confidence interval (CI), 7.2 to 9.3] vs. 5.6 months [95% CI, 4.2 to 6.7]; hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; P<0.001).

VI. Although prior endocrine-based therapy was not required in the EMBRACA trial, 90.4% of patients had progressed on endocrine-based therapy before being treated with talazoparib (Talzenna), and 100% had received prior chemotherapy for HR+ disease. The standard treatment approach for HR+ disease is to first target the hormone pathway (unless considered inappropriate), then consider single agent chemotherapy or PARP inhibitor if there is a progression on endocrine-based therapy.

VII. The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists the PARP inhibitors [talazoparib (Talzenna) and olaparib (Lynparza)] as Category 1 options for previously treated recurrent or metastatic germline BRCA mutated breast cancer. EMBRACA clinical program included 56% patients with ER/PR+, HER2- advanced or metastatic breast cancer, while 44% had triple-negative breast cancer (TNBC). Thus, talazoparib (Talzenna) may be considered a practical treatment option for patients with TNBC. However, presence of germline BRCA1 or BRCA2 mutation is a pre-requisite for initiating treatment with talazoparib (Talzenna).

VIII. In the EMBRACA trial, adverse reactions were reported at a higher incidence in those receiving talazoparib than placebo-chemotherapy arm. Sixty-five percent of patients taking talazoparib versus 50% chemotherapy experienced ADE and dose reductions due to any cause occurred in 53% of talazoparib patients versus chemotherapy patients. Due to the high incidence of this, split fill is applied to the medication upon initial approval.

IX. Dose adjustments are common with talazoparib (Talzenna) as the product is flat priced (i.e., there is a single fixed price for each tablet regardless of dosage strength). When possible, patients should be dose optimized to once a day dosing of an appropriate strength versus allowing multiple tablets of a lower dose.

Investigational or Not Medically Necessary Uses

I. The efficacy and safety of talazoparib (Talzenna) in combination with other chemotherapy or immunotherapy agents have not been evaluated. Talazoparib (Talzenna) is indicated as monotherapy.

II. There is no evidence to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.

III. Due to its mechanism of action, there is interest in using talazoparib (Talzenna) in other cancers such as ovarian cancer, prostate cancer, and lung cancer; however, studies are still ongoing and use outside of BRCA mutated advanced or metastatic breast cancer is considered investigational.

IV. Additionally, there is a lack of evidence supporting the use of talazoparib (Talzenna) in early breast cancer (e.g., neoadjuvant or adjuvant treatment).

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


Related Policies

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin-Dependent Kinase (CDK) 46 Inhibitors</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic, early-stage breast cancer</td>
</tr>
<tr>
<td>alpelisib (Piqray)</td>
<td>PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer</td>
</tr>
<tr>
<td>lapatinib (Tykerb)</td>
<td>Breast cancer, HER2 over expression, advanced or metastatic in combination with capecitabine after prior therapy OR postmenopausal women, in combination with letrozole</td>
</tr>
<tr>
<td>neratinib (Nerlynx)</td>
<td>Breast cancer, early stage, HER2-positive, following trastuzumab OR advanced, metastatic</td>
</tr>
<tr>
<td>olaparib (Lynparza)</td>
<td>Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm)</td>
</tr>
<tr>
<td>tucatinib (Tukysa)</td>
<td>Metastatic breast cancer</td>
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Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streamlined clinical criteria to better reflect our current PARP policies. Removed requirement of HER2-negative disease. Removed confirmation member is not platinum refractory. Removed requirement of maximum number of prior cytotoxic regimens. Improved supporting evidence section for better clinical support. Added related policies.</td>
<td>08/2022</td>
</tr>
<tr>
<td>Previous Reviews</td>
<td>02/2019</td>
</tr>
</tbody>
</table>
tapinarof (Vtama®)
UMP POLICY

Policy Type: PA

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months
  i. One three-month quantity exception approval allowed per lifetime, when applicable criteria are met.

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tapinarof (Vtama)</td>
<td>Plaque Psoriasis</td>
<td>1% topical cream</td>
<td>60 grams/30 days*</td>
</tr>
</tbody>
</table>

*Quantity exceptions not allowed on initial approval

Initial Evaluation

I. Tapinarof (Vtama) cream may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Diagnosis of plaque psoriasis; AND
   C. Treatment with at least one agent from three different topical medication classes below has been ineffective or not tolerated, unless all are contraindicated:
      1. Corticosteroid: High-potency corticosteroid (e.g., betamethasone, clobetasol)
         i. When located on the face or intertriginous areas only, low-potency corticosteroid (e.g., hydrocortisone) accepted
      2. Calcineurin inhibitor: tacrolimus ointment or pimecrolimus cream
      3. Vitamin D analog: calcipotriene cream/ointment or calcitriol ointment
      4. Retinoid: tazarotene cream

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

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.

September 01, 2022
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**
   A. On first renewal: The member has exhibited improvement in extent and/or severity 
of psoriasis; **OR**
   B. Upon subsequent renewals: The member has exhibited continued improvement or 
stability in extent and/or severity of psoriasis; **AND**

III. If quantity requested is greater than 60 grams (1 tube) per 30-day supply, a quantity exception 
will be considered medically necessary when the following are met:
   A. Documentation of current body surface area affected by psoriasis; **AND**
   B. Rationale for need of more than one tube of cream per 30-days; **AND**
   C. Quantity requested does not exceed the amount needed to cover psoriatic lesions 
at a frequency of once daily.

Supporting Evidence

I. Tapinarof (Vtama) cream is a non-steroidal topical medication for the treatment of plaque 
psoriasis and has only been evaluated for safety and efficacy in adults for the treatment of 
plaque psoriasis. Coverage consideration is limited to those 18 years of age or older. It is being 
evaluated in pediatric patients in clinical trials, and use of therapy is best monitored in pediatrics 
and adolescents in a clinical trial setting until sufficient evidence for safety and efficacy in these 
populations is available.

II. Tapinarof (Vtama) cream is being evaluated in clinical trials for other skin conditions (e.g., atopic 
dermatitis); however, safety and efficacy have not been sufficiently demonstrated for any 
condition other than plaque psoriasis. Thus, coverage consideration is limited only to patients 
with a diagnosis of plaque psoriasis.

III. Tapinarof (Vtama) cream was evaluated as monotherapy in two Phase 3 clinical trials, which 
showed improvement in extent and severity of psoriasis as well as improvement in patient 
quality-of-life vs. a placebo vehicle. It was effective and well tolerated when used on the face 
and intertriginous areas. The extent of efficacy as well as safety when used in combination with 
other topical or systemic agents for this condition are currently unknown given the use as 
monotherapy only in clinical trials. Tapinarof (Vtama) cream joins a market of well-established, 
effective, and generic topical treatment options for psoriasis:
   • Topical corticosteroids (TCS) are the mainstay of therapy for plaque psoriasis, with a 
   variety of chemical entities, potencies, and formulations to satisfy patient needs. These 
   are highly effective, and safety concerns or adverse events can be mitigated by proper 
   use (i.e., application to affected areas only), use of products that offer appropriate 
potency for extent/severity/area of the body, and the correct formulation (e.g., foams, 
sprays, oils, or shampoos for scalp involvement). Plaque psoriasis on the face or 
intertriginous areas may require a low potency TCS (e.g., OTC hydrocortisone 1%).
atrophy is a common concern for utilizing TCS for extended durations of time; however, this is rarely a concern when TCS are applied to plaques appropriately (e.g., on active current lesions). For patients that experience quick recurrence of plaques after TCS discontinuation, TCS may be restarted intermittently, or steroid-sparing therapy may be considered, which may have synergistic effects with TCS.

- **Topical calcineurin inhibitors (TCI):** Tacrolimus 0.1% ointment and pimecrolimus 1% cream are the available generic TCI products, and they may be utilized as monotherapy or in combination with other topicals. These are safe and effective and have been evaluated for use on the face and intertriginous areas, as well as, in pediatric patients.

- **Vitamin D analogs:** Calcipotriene and calcitriol are the available generic products, and they may be utilized as monotherapy or in combination with other topicals. Combination use with TCS may have synergistic efficacy and increases tolerability vs. either agent alone. Monotherapy preparations are available, as well as betamethasone dipropionate-calcipotriene as a generic single preparation combination therapy as various formulations. These are applied once daily.

- **Topical retinoid:** Tazarotene 0.05% cream and 0.1% cream and foam are available with the 0.1% products being available as generics. Similar to vitamin D analogs, use with TCS may increase improve efficacy and tolerability. A single preparation combination therapy is available for halobetasol-tazarotene (Duobrii).

IV. Tapinarof (Vtama) cream has not proven to be superior in safety or efficacy to established therapies. Given the lack of definitive clinical advantage, as well as, higher cost relative to available generic therapies, use of at least three different classes of standard of care topical medications is required prior to coverage consideration of tapinarof (Vtama) cream.

V. One tube of tapinarof (Vtama) cream contains 60 grams, which should be adequate to cover 8% of the body surface area on average for 30-days when used appropriately (e.g., thin layer, once daily application). This quantity is likely sufficient for patients that have greater than 10% of the body surface area affected as well, given that when efficacy is realized the quantity needed to cover psoriatic plaques will decrease over time. Not all patients will respond to therapy or be able to tolerate therapy. Given these considerations, the plan’s quantity limit for initial approval (i.e., first six months) is one tube per month, to minimize risk of medication waste as efficacy, tolerability, and adherence are realized. Upon renewal, a quantity exception may be granted based on medical necessity. The current body surface area affected and provider rationale for needing increased quantity will be reviewed relative to the labeled dosing recommendations and frequency. A one-time quantity exception may be granted when criteria are met. In clinical trials for patients that respond to therapy, tapinarof (Vtama) has the potential to treat psoriatic lesions and may prevent occurrence of new lesions for several months follow treatment success. If continuous use at excessive quantities of tapinarof (Vtama) cream are required, alternative treatment strategies with greater potential efficacy and favorable cost effectiveness may be more appropriate (e.g., other topical therapies, DMARDS, other systemic agents).
Investigational or Not Medically Necessary Uses

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

References


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.

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
</tr>
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<tbody>
<tr>
<td>Chronic Inflammatory Disease Policy</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>Systemic Janus Associated Kinase Inhibitors in Chronic Inflammatory Disease Policy</td>
<td>Plaque psoriasis</td>
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Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Policy created</td>
<td>08/2022</td>
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</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP215

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tasimelteon (Hetlioz)</td>
<td>20 mg capsules</td>
<td>Non 24-Hour Sleep-Wake Disorder; Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)</td>
<td>30 capsules/30 days</td>
</tr>
<tr>
<td>tasimelteon (Hetlioz LQ)</td>
<td>4 mg/mL oral suspension</td>
<td>Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)</td>
<td>0.7 mg/kg* 158 ml bottle**</td>
</tr>
</tbody>
</table>

* for members weighing 28kg or less
** for members weighing more than 28kg

Initial Evaluation

I. Tasimelteon (Hetlioz, Hetlioz LQ) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist, sleep specialist, or psychiatrist; AND
   B. Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated, or not tolerated; AND
   C. A diagnosis of Non-24-hour sleep-wake disorder (N24HSWD) when the following are met:
      1. Member is 18 years of age or older; AND
      2. Member has a diagnosis of total blindness in both eyes without light perception; AND
      3. Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days; AND
      4. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or all are contraindicated:
         i. benzodiazepines (eg. flurazepam, lorazepam, temazepam)
         ii. non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon)
         iii. melatonin agonist (eg. ramelteon); OR

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.

September 01, 2022
D. A diagnosis of **Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** when the following are met:
   1. Genetic testing has identified a heterozygous deletion of 17p11.2; **OR**
      i. A heterozygous pathogenic variant involving RAI1; **AND**
   2. Request is for tasimelteon (Hetlioz) capsules; **AND**
      i. Member is 16 years of age or older; **OR**
   3. Request is for tasimelteon (Hetlioz LQ) oral solution; **AND**
      i. Member is between three and 15 years of age; **AND**
      ii. Current weight provided in documentation

II. Tasimelteon (Hetlioz, Hetlioz LQ) is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Sighted individuals with non-24-hour sleep-wake disorder
   B. Non-24-hour sleep-wake disorder in blind individuals with light perception
   C. Jet lag disorder
   D. Major depressive disorder

**Renewal Evaluation**

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g. longer duration of nighttime sleep, more alert during the day]

**Supporting Evidence**

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

o Duration of nighttime sleep was improved by 28 minutes and the duration of daytime napping was reduced by 27 minutes, while each worsened when treatment was withdrawn.

II. There is a lack of randomized clinical trial data to show safety and efficacy of tasimelteon (Hetlioz) in pediatric patients with the diagnosis of N24SWD. Although the SMS indication is approved in pediatric patients – very few pediatric patients (N=11) have actually received the medication, thus, use for N24HSWD in those under 18 years of age would be considered experimental.

III. Per the American Academy of Sleep Medicine Clinical Practice Guideline, a diagnosis of N24SWD requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.

IV. The exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects. The American Academy of Sleep Medicine has identified three studies in their guideline. Melatonin was administered either one hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days (one to three months). The entrainment rate (12 of 18) found in the current meta-analysis of melatonin treatment in N24SWD was 67%. Due to the lack of head-to-head trials there is no clinical trial data to show that one therapy is superior to the other.

V. The safety and efficacy of tasimelteon (Hetlioz) for Nighttime Sleep Disturbances in SMS has been established a pivotal phase 2/3, nine-week, double-blind, randomized, placebo-controlled, two-period crossover study in 14 adults and 11 pediatric patients.

<table>
<thead>
<tr>
<th>Primary Efficacy Measures</th>
<th>Treatment Group</th>
<th>LS Meana (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Average of 50% Worst Daily Nighttime Sleep Quality*</td>
<td>HETLIOZ (n=25)</td>
<td>2.8 (0.15)</td>
<td>0.4 (0.1, 0.7)</td>
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<tr>
<td></td>
<td>Placebo (n=25)</td>
<td>2.4 (0.15)</td>
<td>-</td>
</tr>
<tr>
<td>Average of 50% Worst Daily</td>
<td>HETLIOZ (n=25)</td>
<td>7.0 (0.26)</td>
<td>0.3 (-0.0, 0.6)</td>
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<tr>
<td></td>
<td>Placebo (n=25)</td>
<td>6.7 (0.26)</td>
<td>-</td>
</tr>
</tbody>
</table>
VI. The recommended dosage of tasimelteon (Hetlioz LQ) oral suspension for the treatment of nighttime sleep disturbance in SMS pediatric patients three to 15 years of age is by body weight. For patients with 28 kg or less the recommended dose is 0.7 mg/kg and for patients who weigh more than 28 kg the recommended dose is 20 mg one hour before bedtime.

VII. Smith-Magenis syndrome (SMS) is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with SMS have a deletion of genetic material in each cell from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, is responsible for most of the features of the condition. In most of these cases, the deletion is not inherited, occurring randomly during the formation of eggs or sperm, or in early fetal development.

   o The diagnosis of SMS is established in a proband with suggestive clinical features and one of the following on molecular genetic testing: A heterozygous deletion of 17p11.2 or heterozygous pathogenic variant involving RAI1. When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include chromosomal microarray analysis, single-gene testing, or use of a multigene panel.

VIII. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of Circadian Locomotor Output Cycles Kaput (CLOCK) transcription, a key component of the mammalian circadian oscillator. Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients.

IX. As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Given the very limited experience of tasimelteon (Hetlioz) in pediatric populations, the safety and efficacy profile are largely unknown. Melatonin has a more established safety and efficacy profile and should be considered for use prior to tasimelteon (Hetlioz).

Investigational or Not Medically Necessary Uses

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

   A. Sighted individuals with non-24-hour sleep-wake disorder and non-24-hour sleep-wake disorder in blind individuals with light perception

      i. There no published clinical trial data to show safety and efficacy and support the use of tasimelteon (Hetlioz) in these patient populations.

   B. Jet lag disorder
i. A phase II, randomized, double blind proof of concept study to evaluate the effects of tasimelteon and placebo in travelers with jet lag disorder with the primary outcome measure of changes in sleep after transmeridian travel measured by nighttime sleep parameters

ii. A randomized, double-blind, placebo-controlled, parallel design study evaluating the effects of tasimelteon compared to placebo on jet lag type insomnia enrolled 320 healthy adult patients. Tasimelteon treatment increased Total Sleep Time in the first 2/3 of the night (primary endpoint) by 60.3 min (95%CI 44.0 to 76.7, P < 0.0001) and whole night TST by 85.5 min (95% CI 64.3 to 106.6, P < 0.0001), improved next day alertness, next day sleepiness, and shortened latency to persistent sleep by −15.1 min (95% CI −26.2 to −4.0, P = 0.0081).

iii. Jet Lag was induced by an immediate phase advance of the sleep-wake cycle in a sleep clinic, rather than jet travel in the eastward direction.

iv. There isn’t robust safety and efficacy data to support the use of tasimelteon (Hetlioz) in the treatment of the jet lag disorder.

C. Major Depressive Disorder (MDD)

i. A randomized, parallel, double-masked, placebo-controlled, multicenter outpatient study comparing tasimelteon with placebo with 507 enrolled participants (MAGELLAN) followed by a 52-week open label extension.

   o The primary outcome measure was change from baseline to endpoint at week 8 using the total score of Hamilton Depression Rating Scale (HAM-D) was not met.

   o The clinical trial showed insufficient efficacy and limited safety data.

References

6. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). ClinicalTrials.gov Identifier: NCT01428661

11. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). ClinicalTrials.gov Identifier: NCT01428661


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Added new indication of Nighttime Sleep Disturbances in SMS</td>
<td></td>
</tr>
<tr>
<td>• Added a new formulation, the tasimelteon (Hetlioz LQ) oral solution</td>
<td></td>
</tr>
<tr>
<td>• New criteria added for the indication of N24HSWD:</td>
<td>12/2020</td>
</tr>
<tr>
<td>o Treatment with melatonin (for at least three months continuously) has been ineffective,</td>
<td></td>
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<tr>
<td>contraindicated or not tolerated</td>
<td></td>
</tr>
<tr>
<td>o Member has a diagnosis of total blindness in both eyes without light perception</td>
<td></td>
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<tr>
<td>o Provider has documented progressively shifting sleep-wake times with sleep diaries and/or</td>
<td></td>
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<tr>
<td>actigraphy for at least 14 days</td>
<td></td>
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<tr>
<td>o Treatment with at least TWO alternatives has been ineffective or not tolerated, or all</td>
<td></td>
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<tr>
<td>are contraindicated: benzodiazepines (eg. flurazepam, lorazepam, temazepam), or non-</td>
<td></td>
</tr>
<tr>
<td>benzodiazepines (eg. doxepin, eszopiclone, zaleplon) or melatonin agonist (eg. ramelteon)</td>
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</tr>
<tr>
<td>• Criteria removed from the indication of N24HSWD:</td>
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</tr>
<tr>
<td>o Member has no hepatic impairment or mild to moderate hepatic impairment</td>
<td></td>
</tr>
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<td>o Member is not on concurrent strong CYP3A4 inducers or CYP1A2 inhibitors</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP184

Split Fill Management*

Description
Tazemetostat (Tazverik) is an orally administered inhibitor of methyltransferase, EZH2.

Length of Authorization
- N/A

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tazemetostat (Tazverik)</td>
<td>200 mg tablets</td>
<td>Epithelioid sarcoma, advanced or metastatic, not eligible for resection; Follicular lymphoma, relapsed or refractory, EZH2 mutation-positive, in that that have received at least two therapies; Follicular lymphoma, relapsed or refractory, in those with no satisfactory alternative therapy</td>
<td>240 tablets/30 days</td>
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</table>

Initial Evaluation

I. Tazemetostat (Tazverik) is considered investigational when used for all conditions, including but not limited to:
   A. Epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma

Renewal Evaluation

I. N/A

September 01, 2022
Supporting Evidence

I. Background: Epithelioid sarcoma is a very rare cancer of the soft tissue, generally seen in younger populations (average age of 27). This aggressive condition is known for recurrence, spread to locoregional lymph nodes, and eventually distant metastases. Common sites of origin include fingers, hands, forearms, feet, and other limbs. First-line management is typically surgery, with local recurrence necessitating amputation in many cases. Although, not specifically FDA-approved for epithelioid sarcoma, there are several systemic therapies used in the metastatic setting. Often, anthracycline based regimens (e.g., doxorubicin with or without ifosfamide), gemcitabine, pazopanib (Votrient), doxetaxel, sunitinib (Sutent), dacarbazine, epirubicin, and temozolomide.

II. Efficacy: Tazemetostat (Tazverik) was approved on data from a Phase 2 trial. Pooled data from two cohorts, five and six (n=62, n=44), were used to support the approval. Seventy-seven percent of patients had prior surgery and 61% had prior chemotherapy. Primary outcomes included objective response rate (ORR) assessed every eight weeks and progression-free survival (PFS). Secondary endpoints were duration of response (DOR), disease control rate (DCR) and overall survival (OS). The pooled data showed an objective response rate of 13% (CR 1.6%, PR 11%). Duration of response was 12.8 months (3.5-24 months). Pooled data for progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) were not reported for the pooled data; however, for Cohort 5 PFS was 23.7 weeks, DCR was 21%, and OS was 82 weeks.

III. Safety: There are no contraindications for tazemetostat (Tazverik); however, there is a warning for development of secondary malignancies, such as T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Six out of 668 treated patients had developed secondary malignancy as of quarter May 2019. Common (≥ 20%) adverse reactions noted from the trial included: fatigue, nausea, decreased appetite, vomiting and constipation. One patient in the clinical trial discontinued therapy due to adverse events, 34% required a dose interruption, and there were not deaths from treatment. Tazemetostat (Tazverik) has significant drug interactions with CYP450 inhibitors and inducers, and there is a warming for embryo fetal toxicity and lactation. Due to the limited number of subjects treated and short duration of use, the safety profile of tazemetostat (Tazverik) is largely unknown at this time.

IV. The quality of the evidence is low given the Phase 2, open-label, single-arm trial. The primary endpoints have not been correlated with clinically meaningful outcomes such as improvement in morbidity, mortality or symptom relief, and results have not been confirmed in other studies. Additionally, due to the limited number of subjects treated, the safety profile is highly unknown. Coupled with the low rates of response, there is uncertain usefulness of tazemetostat (Tazverik) at this time.

V. Tazemetostat (Tazverik) was approved under the accelerated approval pathway and orphan drug designation. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

VI. Follicular lymphoma (FL), is an indolent form of NHL that arises from B-lymphocytes. Treatment is dependent on stage, or histologic grade of condition, and may include the following: radiation therapy, immunotherapy, and chemotherapy. In the space of relapsed or refractory to two prior therapies, the PI3K inhibitors are recommended per NCCN (e.g., copanlisib, duvelisib, idelalisib), as well as selinexor.
VII. Tazemetostat (Tazverik) for FL was evaluated for safety and efficacy in one open-label, single-arm, Phase 2 trial at 800 mg twice daily. There were 99 patients included in the trial, 45 of which were EZH2 mutated, and 54 were EZH2 wild type. Patients were adults with confirmed FL (grade 1-3b), relapsed or refractory to two or more standard systemic therapies, with life expectancy of three months or more, and adequate organ function. Some patients had up to five or more previous therapies, and up to 59% were rituximab refractory, up to 28% were double refractory, and up to 29% had hematopoietic stem cell transplant.

VIII. Tazemetostat (Tazverik) was approved under the accelerated approval pathway for FL based on objective response rate, duration or response, and progression free survival. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Treatment emergent adverse events (TEAE) occurred in 99% of patients, and serious AE occurred in 27%. The most common serious AE being sepsis, physical health deterioration, and anemia. Other notable serious AE were neutropenia, pancytopenia, global amnesia, arrhythmia, and myelodysplastic syndrome. Dose reductions due to adverse events as well as dose interruptions occurred at rates of 27%, and 8% of patients permanently discontinued due to AE. One case of AML was reported, and four patients died within 30 days of the last dose of study drug. The study investigators deemed these not related to treatment.

IX. Given the observational nature of the data, true medication safety and efficacy is unknown. Open-label, single-arm trials are insufficient for determining cause and effect of treatment. Additionally, ORR, DoR, and PFS have not been correlated with clinically meaningful outcomes such as improvement in quality of life, symptom control, or overall survival.

Investigational or Not Medically Necessary Uses

I. There is a lack of high-quality data from randomized controlled trials to indicate the safety and efficacy of tazemetostat (Tazverik) in the following indications:
   A. Soft tissue sarcoma, including epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma
   C. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   D. Rhabdoid tumors
   E. Mesothelioma
   F. Kidney, bladder, urothelial cancers
   G. Hepatocellular carcinoma

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


Policy Implementation/Update:

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Washington State Rx Services is administered by moda HEALTH

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.
Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP024

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

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

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<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tr>
<td>teduglutide</td>
<td>5 mg vial kit (one vial)</td>
<td>Short Bowel Syndrome</td>
<td>1 vial/1 day</td>
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<td>(Gattex)</td>
<td>5 mg vial kit (30 vial)</td>
<td>(SBS)</td>
<td>30 vials/30 days</td>
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Initial Evaluation

I. Teduglutide (Gattex) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older and weighs more than 10 kg; AND
   B. Teduglutide (Gattex) has been prescribed by, or consultation with a specialist in gastroenterology; AND
   C. A diagnosis of Short Bowel Syndrome; AND
      1. Member dependence on parenteral nutrition/intravenous support for at least 12 months; AND
      2. Member dependence on parenteral nutrition at least three times a week; AND
      3. Laboratory assessment within the last six months of bilirubin, alkaline phosphatase, lipase and amylase to rule out gallbladder, biliary tract or pancreatic disease; AND
      4. Colonoscopy within the last 6 months to rule out colorectal polyps or small bowel neoplasia in adult members; OR
      5. Fecal occult blood testing in children and adolescents within the last 6 months; AND
         i. Documentation of a follow-up colonoscopy for any positive fecal occult blood test

II. Teduglutide (Gattex) is considered investigational when used for all other conditions, including but not limited to:
A. Crohn’s disease  
B. Enterocutaneous Fistula (ECF)  
C. Gastric emptying

Renewal Evaluation

I. Clinical documentation of response to therapy as demonstrated by:  
   A. Decrease in volume of parenteral or intravenous nutritional support; OR  
   B. Decrease in number of days of parenteral or intravenous nutritional support; AND  
II. Colonoscopy performed within the last 12 months to rule out colorectal polyps or small bowel neoplasia upon first renewal, and, no less than every five years; AND  
III. Bilirubin, alkaline phosphatase, lipase, and amylase laboratory assessment to rule out gallbladder, biliary tract or pancreatic disease within the last six months.

Supporting Evidence

I. Teduglutide (Gattex) is FDA approved for treatment adults and pediatric patients 1 year of age or older with Short Bowel Syndrome (SBS) who are dependent on parenteral support.  
II. The pivotal trial included patients with SBS who were dependent on parenteral nutrition/intravenous support for at least 12 months and at least 3 times per week.  
III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency. The higher dose treatment arm did not demonstrate a statistically significant difference when compared to placebo.  
IV. Colonoscopies should be completed again 1 year after treatment then no less frequently than every 5 years to evaluate for polyps and gastrointestinal malignancies.  
V. Lab assessments are recommended every 6 months to evaluate for gallbladder, biliary tract and pancreatic disease.

Investigational or Not Medically Necessary Uses

I. Crohn’s Disease  
   A. Phase II clinical trials have evaluated teduglutide for the treatment of Crohn’s disease.  
   B. Clinical concerns for the safety of teduglutide in patients with Crohn’s disease include neoplastic growth, intestinal obstruction and biliary and pancreatic disease.  
   C. Large, well-controlled clinical trials are needed to demonstrate benefit of use of teduglutide in patients with Crohn’s Disease.  
II. Clinical trials are ongoing in the following indications:  
   A. Enterocutaneous Fistula (ECF)  
   B. Gastric emptying

References

Policy Implementation/Update:

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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP087

Description
Tegaserod (Zelnorm) is an orally administered serotonin-4 (5-HT4) receptor agonist.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>tegaserod (Zelnorm)</td>
<td>6 mg tablets</td>
<td>Irritable bowel syndrome with constipation</td>
<td>60 tablets/30 days</td>
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</table>

Initial Evaluation

I. Tegaserod (Zelnorm) may be considered medically necessary when the following criteria below are met:
   A. The member is between 18 and 65 years of age; AND
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; AND
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member is female; AND
      2. The member does not have current, or historical, cardiovascular disease; AND
      3. The member has had an inadequate response to the **ALL** of the following, unless all are contraindicated:
         i. Dietary modifications (e.g., removal of offending foods, increased fiber intake) AND increased physical activity; AND
         ii. At least one osmotic laxative (e.g., polyethylene glycol); AND
         iii. Plecanatide (Trulance); AND
         iv. Linaclotide (Linzess); AND
         v. Lubiprostone (Amitiza)

II. Tegaserod (Zelnorm) is considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Irritable bowel syndrome with constipation in males

III. Tegaserod (Zelnorm) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Idiopathic chronic constipation

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.
B. Opioid or other drug induced constipation
C. Gastroesophageal reflux disease (GERD)

**Renewal Evaluation**

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

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

III. The member is between 18 and 65 years of age; **AND**

IV. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**

A. _A diagnosis of irritable bowel syndrome with constipation (IBS-C); AND_
   1. The member does not have a history of, or current cardiovascular disease; **AND**
   2. The member has experienced a response to treatment (e.g. increase in rate of bowel movements)

**Supporting Evidence**

I. Tegaserod (Zelnorm), a serotonin-4 (5-HT4) receptor agonist, is FDA-approved and indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women < 65 years of age. It was originally approved in 2002, for short-term treatment of women with IBS-C; however, it was withdrawn from the market in 2007 due to an unfavorable cardiovascular (CV) and suicidal ideation and behavior (SI/B) safety profile.

II. Efficacy to support reintroduction of tegaserod (Zelnorm) was based on evidence established at the time of original approval and no new evidence on efficacy has been added. Tegaserod (Zelnorm) was evaluated in three multicenter, double-blind, placebo-controlled, 12-week trials of 2,470 women that had at least a three-month history of IBS-C. Response rate (RR) was the primary outcome, and was based on subjective response on a five parameter scale measured each week indicating: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Tegaserod (Zelnorm) had superior response rates compared to placebo ranging from 6 to 28%. Secondary outcomes of pain, discomfort and bloating were evaluated on a six-to-seven-point intensity scale. Positive response, defined as at least a 1-point reduction, was measured to be 1-10% superior for tegaserod (Zelnorm) for abdominal pain or discomfort and 4-11% for bloating. The baseline bowel movement rate averaged 3.8 per week and increased to 6 per week for tegaserod (Zelnorm) and 5.5 for placebo.

III. During clinical trials, responders were defined as participants with complete relief or considerable relief for at least two of the four weeks, or somewhat relieved for all of the four weeks (after one month of treatment). It is recommended to assess response to treatment after four to six weeks of treatment, and to discontinue tegaserod (Zelnorm) for nonresponsive patients.

IV. Tegaserod (Zelnorm) is contraindicated in those with established CV history (specifically, myocardial infarction, stroke, transient ischemic attach, angina), renal impairment, hepatic impairment, bowel obstruction, gallbladder disease, suspected sphincter of Oddi dysfunction, or...
abdominal adhesions. Warnings and precautions include CV ischemic events, major adverse CV events (MACE), ischemic colitis, volume depletion with diarrhea, and SI/B. Common adverse effects (≥ 2%) include headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness. Approval of tegaserod (Zelnorm) reintroduction was supported by a complete safety review by the FDA and FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). Retrospective analyses of pooled data from 18,645 patients in 29 placebo-controlled trials in various disease states of at least four weeks duration were included. The imbalance in CV events was measured to be 0.1% for tegaserod (Zelnorm) versus 0.01% in placebo. There was one death, attributed to suicide, during the trial; although, the member had a history of mild depression. The rate of SI/B is measured to be 0.07% for tegaserod (Zelnorm) vs. 0.02% for placebo.

V. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS recommend use of guanylate cyclase activators (e.g. linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g. lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. Tegaserod (Zelnorm) may be considered a subsequent-line therapy based on a conditional recommendation (low quality of evidence) from ACG review panel. Thus, due to the limited efficacy and concerning safety profile, tegaserod (Zelnorm) should only be reserved for those that have exhausted other treatment options.

Investigational or Not Medically Necessary Uses

I. Irritable bowel syndrome with constipation (IBS-C) in males
   A. Two randomized, placebo-controlled, double-blind trials of 288 men did not show differences in efficacy of tegaserod (Zelnorm) versus placebo. This information is stated in the product labeling.

II. Clinical trials are underway, but have not yet been completed to provide insight to safety and efficacy of tegaserod (Zelnorm) in the following settings:
   A. Idiopathic chronic constipation
   B. Opioid or other drug induced constipation
   C. Gastroesophageal reflux disease (GERD)

References

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.

6. FDA Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Briefing Document; Sloan Pharma; US WorldMeds, 10/17/2018; accessed via https://www.fda.gov/media/119013/download


**Policy Implementation/Update:**

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<td>Policy updated to require trials of Trulance, Linzess, AND Amitiza for coverage consideration of Zelnorm; updated supporting evidence to reflect 2021 ACG guideline recommendations; made minor formatting changes to align policy with current format; <strong>(Effective 7/1/2021)</strong></td>
<td>05/2021</td>
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<td>08/2019</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP155

Description
Telotristat ethyl (Xermelo) is an orally administered tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

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<td>(Xermelo)</td>
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<td>Diarrhea</td>
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Initial Evaluation
I. Telotristat ethyl (Xermelo) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, oncologist or gastroenterologist; **AND**
   C. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]); **AND**
   D. A diagnosis of **carcinoid syndrome diarrhea** when the following are met:
      1. Clinical documentation of significant diarrhea (≥ 4 bowel movements per day on average); **AND**
      2. Treatment with a somatostatin analog therapy (e.g. octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]) has not been effective after at least 3 months of therapy, was not tolerated, or is contraindicated.

II. Telotristat ethyl (Xermelo) is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer

Renewal Evaluation

Washington State Rx Services is administered by moda HEALTH

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.

September 01, 2022
I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Member has exhibited improvement or stability of disease symptoms defined by a decrease in overall average bowel movements per week from baseline; AND
IV. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]).

Supporting Evidence

I. The safety and efficacy for telotristat ethyl (Xermelo) was studied in a 12-week double-blind, placebo-controlled, randomized, multicenter trial in adult patients with well differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months. The primary efficacy outcome was the change from baseline in the number of daily bowel movements averaged over the 12-week treatment period; in the telotristat ethyl (Xermelo) arm, there was a reduction of -1.4 bowel movements per day compared to -0.6 in the placebo arm with p<0.001.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer/Other Neuroendocrine Tumors (NETs)

References


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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP163

Description
Temozolomide is an alkylating agent that undergoes rapid nonenzymatic conversion to the reactive compound 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be caused primarily by alkylation of DNA. Alkylation (methylation) occurs mainly at the O\textsuperscript{6} and N\textsuperscript{7} positions of guanine which leads to DNA double strand breaks and apoptosis.

Length of Authorization
- Initial: Three months
- Renewal: Six months

Quantity Limits

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Provider Administered Agents*

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*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. Temozolomide (Temodar) may be considered medically necessary when treatment with generic temozolomide has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation
I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

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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.
Policy Type: PA/SP
Pharmacy Coverage Policy: UMP170

Description
Tenapanor (Ibsrela) is an orally administered sodium/hydrogen exchange 3 (NHE3) inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenapanor (Ibsrela)</td>
<td>50 mg tablets</td>
<td>Irritable bowel syndrome with constipation (IBS-C)</td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. **Tenapanor (Ibsrela)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member has had an inadequate response, or intolerance to, **ALL** of the following, unless all are contraindicated (*Please note: These agents may be subject to additional prior authorization review):
         i. Dietary and lifestyle modifications (e.g., removal of offending foods, increased fiber intake) and increased physical activity; **AND**
         ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
         iii. plecanatide (Trulance); **AND**
         iv. linaclotide (Linzess)*; **AND**
         v. lubiprostone (Amitiza)*

II. **Tenapanor (Ibsrela)** is considered **investigational** when used for all other conditions, including but not limited to:
   A. Hyperphosphatemia
   B. Chronic kidney disease
   C. Irritable bowel syndrome with diarrhea
   D. Mixed irritable bowel syndrome
   E. Chronic idiopathic constipation
   F. Opioid-induced constipation
Renewal Evaluation

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

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

III. The member has exhibited response to the treatment (e.g., improvement in complete spontaneous bowel movements per week from baseline, reduction in abdominal pain)

Supporting Evidence

I. Tenapanor (Ibsrela) is approved by the US Food and Drug Administration (US-FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

II. Given the complexities involved in diagnosis and management of IBS-C, as well as required monitoring for adverse events and therapy response, therapy decisions regarding initiation of tenapanor (Ibsrela) must be made by, or under the supervision of, a specialist practicing in this setting (e.g., gastroenterologist).

III. Tenapanor (Ibsrela) is a sodium/hydrogen exchange 3 (NHE3) inhibitor acting specifically in the GI tract, with minimal systemic availability following oral administration. Inhibition of NHE3 leads to a reduction in dietary sodium absorption and an increase in intracellular protons across membranes in the GI tract, which results in reduction of phosphate absorption from the small intestine and colon. Additionally, consequent increase in sodium and phosphorus content in the stool, decreased urinary sodium and phosphorus excretion, and increased water secretion into the intestinal lumen and the increased stool water content leads to loosened stool consistency and increased bowel movement frequency.

IV. Tenapanor (Ibsrela) has a Black Box Warning for serious dehydration in pediatric patients and has not been evaluated in any pediatric population to date. It is contraindicated in those less than six years of age and comes with a recommendation to avoid use in those less than 12 years of age due to animal studies showing cause of death to be dehydration in young juvenile rats. Additionally, tenapanor (Ibsrela) is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

V. Tenapanor (Ibsrela) was evaluated in two double-blind, placebo-controlled, randomized trials in adult patients –T3MPO-2 and T3MPO-1. The majority of subjects were female (83%), white, and all met Rome III criteria for IBS-C. This requires a pain score of at least three on a 0-10 scale, less than three complete spontaneous bowel movements (CSBM) per week, and less than five spontaneous bowel movements (SBM) per week.

- The primary outcome was proportion of responders, defined as achieving both of the following for at least six of the first 12 weeks of the trials: an increase of at least one CSBM per week on average and a reduction of 30% in weekly average abdominal pain score compared to baseline.

- T3MPO-2: 620 subjects were evaluated for 26 weeks of treatment. Responders active vs. placebo: 37% vs. 24% (CI 6-20%). Difference from placebo 13%.
T3MPO-1: 606 subjects were evaluated for 12 weeks and then were re-randomized to active drug or placebo for a 4-week withdrawal period. Responders active vs. placebo: 27% vs. 19% (CI: 2-15%). Difference from placebo 8%.

VI. The quality of the evidence is considered low given the invalidated subjective endpoints used to determine efficacy and the short duration of therapy evaluated for safety and efficacy.

VII. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS-C recommend use of guanylate cyclase activators (e.g., linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g., lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. As of March 2022, the ACG guidelines do not include tenapanor (Ibsrela) as a recommended agent for the treatment of IBS-C. Based on the clinical evidence showing limited treatment effect and lack of place in therapy information, usability of tenapanor (Ibsrela) is uncertain at this time. Thus, use of non-pharmacologic agents and other established therapies are warranted prior to payment consideration for tenapanor (Ibsrela).

Investigational or Not Medically Necessary Uses

I. Safety and efficacy have not yet been sufficiently established and/or clinical trials are currently underway for the following indications:
   A. Hyperphosphatemia
   B. Chronic kidney disease
      i. Tenapanor (Ibsrela) was evaluated for the treatment of hyperphosphatemia associated with chronic kidney disease (CKD). On July 29, 2021, the US-FDA issued a complete response letter (CRL) regarding the New Drug Application (NDA) for tenapanor for the control of serum phosphorus levels in patients with CKD on dialysis. In the CRL, while the FDA agreed that “the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis,” the agency found the treatment effect was “small and of unclear significance.” Additionally, the FDA indicated to the need to “conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorous or an effect on the clinical outcome thought to be caused by hyperphosphatemia in CKD patients on dialysis”. It is unclear if or when the US-FDA approval for tenapanor (Ibsrela) may be granted for this indication.

II. Tenapanor (Ibsrela) has not been evaluated and/or approved for the treatment of following indications:
   A. Irritable bowel syndrome with diarrhea
   B. Mixed irritable bowel syndrome
   C. Chronic idiopathic constipation
   D. Opioid-induced constipation
References


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.

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
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<tbody>
<tr>
<td>Tegaserod (Zelnorm) Policy</td>
<td>Irritable bowel syndrome with constipation (IBS-C)</td>
</tr>
<tr>
<td>Opioid-Induced Constipation Policy</td>
<td>Opioid-induced constipation</td>
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Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Policy updated to include pre-requisites of trial of current formulary and preferred agents; removed criteria requiring documentation of pain scores and stool frequency; updated supporting evidence</td>
<td>03/2022</td>
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<td>Policy created</td>
<td>02/2020</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP221

Split Fill Management*

Description
Tepotinib (Tepmetko) is an orally administered tyrosine kinase inhibitor (TKI) that targets mesenchymal-epithelial transition (MET).

Length of Authorization
- N/A

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>tepotinib (Tepmetko)</td>
<td>225 mg tablets</td>
<td>Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping</td>
<td>60 tablets/30-day supply</td>
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</table>

Initial Evaluation
I. Tepotinib (Tepmetko) is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung Cancer.

Renewal Evaluation
I. N/A

Supporting Evidence
I. Tepotinib (Tepmetko) is a tyrosine kinase inhibitor that targets mesenchymal-epithelial transition (MET) and is currently being evaluated in Non-Small Cell Lung Cancer (NSCLC) that contains a mutation that leads to MET exon 14 skipping. The clinical trial dose is 500 mg orally once daily.

II. Tepotinib (Tepmetko) is the second therapy FDA-approved for this specific NSCLLC mutation, joining capmatinib (Tabrecta). Other therapies that have been utilized in this setting include crizotinib (Xalkori), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., pembrolizumab); however, available data to support efficacy in this population is limited, and response to therapy is generally poor.
III. Place in therapy is likely to be in the advanced or metastatic setting based on the population being evaluated in the clinical trial, and may be utilized as first-line in these stages; however, given the limited safety and efficacy data to support its use, other therapies may be considered prior to tepotinib (Tepmetko). As of October 2020, the NCCN treatment guidelines had not yet included tepotinib (Tepmetko). Tepotinib (Tepmetko) is mentioned in the ESMO treatment guideline as a treatment option for this population, alongside capmatinib (Tabrecta) and investigational agent savolitinib.

IV. The pivotal trial for tepotinib (Tepmetko) is the VISION trial, which is an open-label, Phase 2, multi-cohort, single-arm, ongoing trial. Patients with MET exon 14 skipping mutations or MET-amplified disease across various treatment settings (e.g., treatment naïve vs. pretreated) were included in the trial. Patients were negative for EGFR mutations or ALK rearrangements, and those with brain metastases were allowed. Ninety-nine patients are being evaluated for efficacy, and the safety profile is based on 152 patients. The average patient age was 74 years, 97% had metastatic disease, 43% were treatment naïve in the advanced/metastatic setting, 33% received one prior therapy, and 11% had two or more prior therapies. Japanese patients were excluded, due to an ongoing trial specific to that population.

V. Objective response was seen in 46 patients (46%), all of which were partial responses. Duration of response was 11.1 months, progression-free survival was 8.5 months, overall survival 17.1 months, and EORTC-QLQ-LC13 cough symptom quality of life scores showed a 13-15 point reduction.

VI. Tepotinib (Tepmetko) was granted Breakthrough Therapy designation, Priority Review, and is being evaluated under FDA Real-Time Oncology Review (RTOR) pilot program – intended to be a more efficient review process to bring safe and effective treatment to patients as early as possible. The application is supported by the results of the Phase 2, ongoing VISION study that has shown potential anti-tumor activity via response rate.

VII. True medication safety and efficacy of tepotinib (Tepmetko) remain unknown given the observational nature of the trial (i.e., lack of comparator arm and open-label study design).

VIII. Safety of tepotinib (Tepmetko) has been evaluated in 152 patients, with a median exposure of 6.9 months. Eighty-nine percent of patients experienced treatment related adverse events (AE). Common AE were peripheral edema (63%), nausea (26%), diarrhea (26%), creatinine increase (18%), hypoalbuminemia (16%), amylase increase (11%), lipase increase (9%), asthenia (8%), anorexia (8%), pleural effusion (8%), and alopecia (8%).

IX. Grade 3 or 4 AE occurred in 28% of patients, mainly peripheral edema and amylase and lipase increases. Serious AE’s occurred in 15%, 11% permanently discontinued due to AE’s overall, and 33% of patients had a dose reduction due to AE’s. Peripheral edema was the most common reason for discontinuation or dose reduction. Sixteen percent of patients had dose reduction and 18% had dose interruption based on this AE alone. Twenty-one patients had an AE leading to death while on tepotinib (Tepmetko), one of which was due to interstitial lung disease determined as related to tepotinib (Tepmetko) therapy. Currently there is unknown clinical benefit/value of tepotinib (Tepmetko), and the safety risks are outweighing until further evidence is available to support safety and efficacy of tepotinib (Tepmetko). Of note, tepotinib (Tepmetko) is in several ongoing clinical trials alone and in combination with other chemotherapeutic agents for NSCLC.
X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Tepotinib (Tepmetko) has not been sufficiently studied for safety and efficacy for any condition to date.

* 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
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<tr>
<td>Policy created</td>
<td>02/2021</td>
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</tbody>
</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP157

Description

Tetrabenazine (Xenazine®), deutetrabenazine (Austedo™) and valbenazine (Ingrezza™) are reversible vesicular monoamine transporter 2 (VMAT2) inhibitors that act by regulating monoamine uptake from the cytoplasm to the synaptic vesicle. Its mechanism of action in Tardive dyskinesia or chorea-reduction is unknown.

Length of Authorization

- Initial (Tardive dyskinesia): Three months
- Initial (Chorea associated with Huntington’s disease): 12 months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetrabenazine (Xenazine)</td>
<td>12.5 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td>60 tablets/30 days</td>
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<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease, genotyped extensive and intermediate metabolizers</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>generic tetrabenazine</td>
<td>12.5 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease, genotyped extensive and intermediate metabolizers</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>deutetrabenazine (Austedo)</td>
<td>6 mg</td>
<td>Tardive dyskinesia in adults; Chorea associated with Huntington’s disease</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>9 mg</td>
<td></td>
<td>120 tablets/30 days</td>
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<td></td>
<td>12 mg</td>
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<tr>
<td>valbenazine (Ingrezza)</td>
<td>40 mg</td>
<td>Tardive Dyskinesia</td>
<td>30 capsules/30 days; 4-week Initiation Pack</td>
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<tr>
<td></td>
<td>80 mg</td>
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</table>
Initial Evaluation

I. Tetrabenazine (Xenazine), deutetetrabenazine (Austedo) and valbenazine (Ingrezza) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist or psychiatrist; **AND**
   C. Medication will **not** be used in combination with another VMAT2 inhibitor [e.g. tetrabenazine (Xenazine), deutetetrabenazine (Austedo) valbenazine (Ingrezza)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
   D. A diagnosis of one of the following:
      1. **Chorea associated with Huntington's disease; AND**
         i. Prior treatment with at least one standard-of-care therapy for the treatment of chorea (e.g. amantadine, olanzapine, risperidone, aripiprazole, riluzole, haloperidol, fluphenazine) has been ineffective, unless all are contraindicated or not tolerated; **AND**
         ii. Member has been tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6 (see quantity limit table based on metabolizer status); **AND**
         iii. **For deutetetrabenazine (Austedo) only:** Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iv. **For Tetrabenazine (Xenazine) only:** Treatment with generic tetrabenazine and deutetetrabenazine (Austedo) has been ineffective, contraindicated or not tolerated; **OR**
      2. [For generic tetrabenazine, valbenazine (Ingrezza) and deutetetrabenazine (Austedo) only] **Tardive dyskinesia; AND**
         i. At least one of the following treatment approaches was ineffective, unless all are contraindicated, not tolerated, or put psychiatric stability at risk:
            a. Switching from a first-generation neuroleptic (e.g. fluphenazine, haloperidol, loxapine, perphenazine, trifluoperazine) to a second-generation neuroleptic (e.g. clozapine, risperidone, olanzapine, quetiapine); **OR**
            b. Member has history of discontinuation or dose modification of the offending medication; **OR**
            c. Member has been trialed on at least one standard therapy (e.g tetrabenazine, amantadine, benzotropine, benzodiazepine) for symptomatic treatment of tardive dyskinesia; **AND**
         ii. **For valbenazine (Ingrezza) only:** Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iii. **For deutetetrabenazine (Austedo) only:** Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated

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.
II. Tetrabenazine (Xenazine) and deutetrabenazine (Austedo) are considered investigational when used for all other conditions, including but not limited to:
   A. Tourette’s syndrome

III. Valbenazine (Ingrezza) is considered investigational when used for all other conditions, including but not limited to:
   A. Chorea associated with Huntington’s disease
   B. Tourette’s syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Safety and effectiveness in pediatric patients has not been established.
II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) need to be prescribed by a neurologist or psychiatrist considering the serious adverse effects (depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability), complexity of the disease state and dosing of the medication.
III. Concomitant use of tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) should not be used in combination with an MAOI.
IV. The American Academy of Neurology (AAN) recommends the use of tetrabenazine (Xenazine), amantadine, or riluzole when medication therapy for chorea is warranted. Per the Physician’s Guide to the Management of Huntington’s Disease 3rd edition, providers often treat chorea with neuroleptics (e.g. aripiprazole, haloperidol, fluphenazine, risperidone, olanzapine) based on clinical experience and due to safety concerns associated with VMAT2-inhibitors, namely: decreased cognition and mood, increased suicidality and depression. Studies of the anti-choreic effects of neuroleptics were excluded from the AAN guideline review due to criteria set forth; however, the AAN acknowledges neuroleptics are commonly used in clinical practice to treat chorea and recommends additional study in recognition of this use. In consideration of the Boxed Warnings and adverse effects associated with this class, a trial of therapy often considered in standards-of-care is reasonable.
V. No sufficient evidence was found to show superiority of one agent over the other.
VI. When clinically appropriate, the two main strategies of pharmacotherapy in patients who are showing signs of tardive dyskinesia include discontinuation of the offending drug and switching
from a first- to a second-generation antipsychotic drug because second generation neuroleptics have a lower risk of TD.

VII. Additional pharmacologic options [e.g. benzodiazepines, anticholinergic drugs (trihexyphenidyl, benztrpine)] have been used in clinical practice for many years. AAN states use of benzodiazepines and tetrabenazine (Xenazine) as standard of care treatments is based on weak clinical evidence but it has been standard of care.

VIII. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other. There is history of use with tetrabenazine in tardive dyskinesia.

IX. For patients with a diagnosis of TD, additional pharmacologic interventions include the use of benzodiazepines, botulinum toxin injections, or tetrabenazine (Xenazine) to control symptoms of TD, paradoxically, resuming treatment with antipsychotic drugs in order to suppress TD.

Investigational or Not Medically Necessary Uses

I. Tourette’s syndrome
   A. Tetrabenazine (Xenazine)
      A. VMAT2 inhibitors currently available in the United States include deutetrabenazine and valbenazine. Although both are being investigated in the treatment of TS, they, like tetrabenazine (Xenazine), are not yet approved by the US Food and Drug Administration (FDA).
      B. There is insufficient evidence to support the use of tetrabenazine (generic, Xenazine) for the treatment of other movement disorders, including, but not limited to dystonic tremor, or Tourette’s syndrome.
   B. Deutetrabenazine (Austedo)
      i. Deutetrabenazine (Austedo) is currently being investigated for use in Tourette’s syndrome in:
         a. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome
         b. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents
      ii. Although deutetrabenazine (Austedo) is being studied for the treatment of Tourette’s syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.
   C. Valbenazine (Ingrezza)
      1. Valbenazine (Ingrezza) is currently being investigated for use in Tourette’s syndrome; however, initial studies have not demonstrated efficacy for this condition.
         i. In a phase 2 trial in pediatric patients with tics associated with Tourette’s syndrome, valbenazine (Ingrezza) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine (Ingrezza) in the Yale Global Tic Severity Scale (YGTSS) at week six in the intent-to-treat population.
         ii. Based on the above results, a second phase 2 trial will aim to evaluate a higher dose of valbenazine (Ingrezza) to suppress tics in pediatric patients.
2. Although valbenazine (Ingrezza) is being studied for the treatment of Tourette’s syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

II. Chorea associated with Huntington’s disease
   A. Valbenazine (Ingrezza) is currently being investigated for use in Chorea associated with Huntington’s disease in a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with Huntington’s disease.

References

1. Austedo [Prescribing Information]. Teva Pharmaceuticals USA, Inc.: North Wales, PA. April 2017
3. Ingrezza [Prescribing Information]. Neurocrine Pharmaceuticals; San Diego, CA. April 2017

Policy Implementation/Update:

<table>
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<th>December 2019</th>
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<td>Last Updated</td>
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<td>Last Reviewed</td>
<td>05/2017, 06/2017, 08/2019, 09/2017, 12/2019</td>
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Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
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<thead>
<tr>
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<th>Date</th>
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<tr>
<td>• Updated criteria to policy format and combined separate polices into one</td>
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<tr>
<td>• Generic tetrabenazine added to tardive dyskinesia criteria</td>
<td></td>
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<tr>
<td>• For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated</td>
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<tr>
<td>• Medication will not be used in combination with another VMAT2 inhibitor, monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine], it is contraindicated</td>
<td>12/2019</td>
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<td>Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)</td>
<td>09/2017</td>
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<tr>
<td>Updated question 5 for valbenazine (Ingrezza™) based on P&amp;T recommendations</td>
<td>08/2017</td>
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tiopronin (Thiola®; Thiola EC®)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP158

Description
Tiopronin (Thiola) is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form tiopronin-cystine disulfide, which is more water soluble than cystine. As a result, the amount of sparingly soluble cystine in the urine is decreased and the formation of cystine calculi is reduced.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tiopronin (Thiola)</td>
<td>100 mg tablet</td>
<td>Nephrolithiasis (cystine), prevention</td>
<td>450 tablets/30 days</td>
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<tr>
<td>tiopronin (Thiola EC)</td>
<td>100 mg delayed release tablet</td>
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<td>450 tablets/30 days</td>
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<tr>
<td></td>
<td>300 mg delayed release tablet</td>
<td></td>
<td>150 tablets/30 days</td>
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</table>

Initial Evaluation
I. Tiopronin (Thiola; Thiola EC) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; OR
      1. Younger than 18 years of age and weighing 20 kg or greater; AND
   B. Medication is prescribed by, or in consultation with, a nephrologist or urologist; AND
   C. A diagnosis of severe homozygous cystinuria when the following are met:
      1. Urinary cystine levels greater than 500 mg/day; AND
      2. Member has not been responsive to all of the following:
         i. High fluid intake
         ii. Urinary alkalinization
         iii. Diet modification (e.g. restriction of sodium and protein intake)

II. Tiopronin (Thiola; Thiola EC) is considered investigational when used for all other conditions.

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

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.
III. Member has exhibited improvement or stability of disease symptoms as indicated by a reduction in cystine stone production OR a urinary cystine concentration less than 250 mg/L.

Supporting Evidence

I. Tiopronin (Thiola; Thiola EC) is a reducing-agent that helps form tiopronin-cystine disulfide, which is more readily excreted by the body, as it is more water soluble.

II. Topronin (Thiola; Thiola EC) is FDA-approved to prevent cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are unresponsive to high fluid intake, alkali, and diet modification.

III. The recommended initial dose in adult patients is 800 mg/day. In clinical studies, the average dose was about 1,000 mg/day.

IV. The recommended initial dose in pediatric patients 20 kg and greater is 15 mg/kg/day. Doses greater than 50 mg/kg per day should be avoided in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day are at greater risk of proteinuria and nephrotic syndrome.

V. Tiopronin (Thiola; Thiola EC) tablets are not approved for use in pediatric patients weighing less than 20 kg as safety and efficacy has not been established in this population.

VI. Urinary cystine levels should be measured one month after initiation of tiopronin (Thiola; Thiola EC) and every three months thereafter. The dose should be adjusted to maintain a urinary cystine concentration of less than 250 mg/L.

Investigational or Not Medically Necessary Uses

I. Tiopronin (Thiola; Thiola EC) has not been sufficiently evaluated outside of severe homozygous cystinuria.

References


Policy Implementation/Update:

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<th>December 2019</th>
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<tr>
<td>Date Effective</td>
<td>December 2019</td>
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<tr>
<td>Last Updated</td>
<td>December 2019</td>
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<td>12/2019</td>
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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.

September 01, 2022
Policy Type: PA
Pharmacy Coverage Policy: UMP229

Description
Tirbanibulin (Klisyri) is a topical microtubule inhibitor.

Length of Authorization
- Initial: One-time fill
- Renewal: Not eligible/Cannot be renewed

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>tirbanibulin (Klisyri)</td>
<td>2.5 mg/250 mg (1%) ointment in a single-dose packet</td>
<td>actinic keratosis (AK)</td>
<td>5 packets/5 days</td>
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</tbody>
</table>

Initial Evaluation

I. Tirbanibulin (Klisyri) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist; **AND**
   C. Member has not been treated with tirbanibulin (Klisyri) before; **AND**
   D. A diagnosis of **actinic keratosis (AK)** when the following are met:
      1. Member will treat lesions on the face or scalp; **AND**
      2. Treatment with at least **TWO** of the following have been ineffective, not tolerated, or all are contraindicated:
         i. 5-fluorouracil (5-FU) cream
         ii. Imiquimod cream
         iii. Diclofenac gel

II. Tirbanibulin (Klisyri) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Patients with recurrent AK previously treated with tirbanibulin (Klisyri)
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp

Supporting Evidence

I. The safety and efficacy of tirbanibulin (Klisyri) has been studied in adult patients, with no clinical trial data to support the use in pediatric patients; however, AK is a skin condition generally seen in the older population.

II. AK is the most common precancer that forms on skin damaged by chronic exposure to ultraviolet (UV) rays from the sun or indoor tanning. Most AKs do not progress to squamous cell
cancer (SCC), but majority of cutaneous SCCs progress from AKs. Given AK may progress to SCC, dermatologist involvement in the patient’s care is recommended.

III. Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment of tirbanibulin (Klisyri). The safety and efficacy of treating with a second application (i.e., treating AK that has recurred after treatment with tirbanibulin [Klisyri]) is unknown.

IV. The safety and efficacy of tirbanibulin (Klisyri) was studied in two identically designed Phase 3, double-blind, vehicle-controlled, randomized, parallel-group, multicenter studies in 702 patients with AK of the face or scalp.

- The majority of patients were white and male, with a Fitzpatrick skin type of I (pale white skin, blue/green eyes, blond/red hair) or II (fair skin, blue eyes) and a median of six lesions.
- The primary efficacy outcome was complete response rate and the main secondary outcome was partial response.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Trial 1 (N=351)</th>
<th>Trial 2 (N=351)</th>
<th>Pooled data (N=702)</th>
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<tr>
<td></td>
<td>tirbanibulin</td>
<td>vehicle</td>
<td>tirbanibulin</td>
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<tr>
<td></td>
<td>(N=175)</td>
<td>(N=176)</td>
<td>(N=178)</td>
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<tr>
<td>Complete response rate*</td>
<td>77 (44%)</td>
<td>8 (5%)</td>
<td>97 (54%)</td>
</tr>
<tr>
<td>Difference</td>
<td>40%</td>
<td>42%</td>
<td>41%</td>
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<tr>
<td>95% CI (32-47); p &lt;0.001</td>
<td>95% CI (33-51); p &lt;0.001</td>
<td>95% CI (35-47); p &lt;0.001</td>
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<tr>
<td>Partial Response rate**</td>
<td>119 (68%)</td>
<td>29 (16%)</td>
<td>136 (76%)</td>
</tr>
<tr>
<td>Difference</td>
<td>52%</td>
<td>57%</td>
<td>54%</td>
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<tr>
<td>95% CI (43-60); p &lt;0.001</td>
<td>95% CI (48-65); p &lt;0.001</td>
<td>95% CI (48-60); p &lt;0.001</td>
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</table>

* Proportion of subjects achieving complete clearance of all AK in the selected area
** Proportion of subjects achieving reduction of at least 75% in the number of lesions within the application area

- Tirbanibulin (Klisyri) treated patients who achieved CR (N=174) were included in a one year follow up; of those, 124 (73%) patients developed lesions within the area treated with tirbanibulin (Klisyri). Out of the 124 patients, 72 (58%) had recurrent lesions and 52 (42%) had new lesions. The sustained complete clearance is 27%.

- The most common local reactions were erythema (91% of the patients) and flaking or scaling (82%). Although generally mild, crusting, swelling, vesiculation or pustulation, erosion, and ulceration were also seen.

V. Longstanding therapies for the treatment of AK include destructive therapies [e.g., surgery, cryotherapy, dermabrasion, photodynamic therapy (PDT)], field ablation treatments (e.g., chemical peels, laser resurfacing), and topical medications (e.g., fluorouracil, imiquimod, diclofenac).

- Topical medications including fluorouracil, imiquimod and diclofenac are used as first-line therapy with a well-established long-term efficacy and safety profile.
- In a randomized controlled trial comparing the recurrence of AKs after treatment with fluorouracil 5%, imiquimod 5%, or PDT, fluorouracil had the highest cumulative probability of remaining free from treatment failure (defined as <75% reduction in AK lesions) 12 months after treatment. For fluorouracil, 75% of patients were free from treatment failure, followed by imiquimod at 54%, PDT at 38%.
- Tirbanibulin (Klisyri) is a topical ointment applied once daily for five consecutive days. Patients who were previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle
of tirbanibulin (Klisyri) and had a high recurrence rate (73%) one year after treatment. There is limited data on long-term safety and efficacy.

**Investigational or Not Medically Necessary Uses**

I. Tirbanibulin (Klisyri) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Patients previously treated with tirbanibulin (Klisyri): Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle of tirbanibulin (Klisyri). The safety and efficacy of treating more than one 25cm² area at a time or as a second application in an area with recurrence is unknown. There is no clinical trial data to support the use in patients previously treated.
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp: The safety and efficacy of tirbanibulin (Klisyri) was studied in patients with AK of the face or scalp. No patients with lesions on other body parts were included in the clinical trial. There is no clinical trial data to support the use on other parts of the body.

**References**


**Policy Implementation/Update:**

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<td>Policy created</td>
<td>05/2021</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP230

Description
Tivozanib (Fotivda) is an orally administered VEGFR kinase inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

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<td>tivozanib (Fotivda)</td>
<td>1.34 mg capsules</td>
<td>Relapsed or refractory advanced renal cell carcinoma, following at least two prior systemic therapies</td>
<td>21 capsules/28 days</td>
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<td></td>
<td>0.89 mg capsules</td>
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Initial Evaluation

I. **Tivozanib (Fotivda)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Not used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus [Torisel], ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
   D. A diagnosis of **advanced or metastatic renal cell carcinoma** when the following are met:
      1. Provider attestation the member has clear cell component histology; **AND**
      2. Member has renal cell carcinoma that is relapsed or refractory to at least **TWO** prior systemic therapies (e.g., axitinib [Inlyta], ipilimumab [Yervoy], nivolumab [Opdivo], everolimus [Afinitor]; **AND**
         i. At least **ONE** of the prior therapies is an anti-VEGFR TKI (e.g., axitinib [Inlyta], lenvatinib [Lenvima], pazopanib [Votrient], sunitinib [Sutent], cabozantinib [Cabometyx].

II. Tivozanib (Fotivda) is considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Renal cell carcinoma prior to third-line treatment

III. Tivozanib (Fotivda) is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Renal cell carcinoma in combination with other oncolytic therapies

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September 01, 2022
B. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
C. Prostate cancer
D. Breast cancer
E. Ovarian, fallopian tube, or primary peritoneal cancer
F. Lung Cancer
G. Gastrointestinal tumors
H. Hepatocellular carcinoma
I. Cholangiocarcinoma
J. Colorectal cancer
K. Glioblastoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Provider attestation the medication will not be used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus [Torisel], ipilimumab [Yervoy], nivolumab [Opdivo]; AND
IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Tivozanib (Fotivda) is a VEGFR tyrosine kinase inhibitor (TKI) that is FDA-approved for patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more systemic therapies. Tivozanib (Fotivda) is approved for 21 days on therapy and seven days off until disease progression or unacceptable toxicity. It is the first therapy specifically FDA-approved for the third-line setting, but joins several other anti-VEGFR medications for this condition, as well as immunotherapies and mTOR inhibitors. All therapy categories are utilized in the subsequent treatment setting after members have progressive disease.

II. Other anti-VEGFR medications include: cabozantinib (Cabometyx), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), sunitinib (Sutent) and axitinib (Inlyta). Immunotherapy options include: ipilimumab (Yervoy), nivolumab (Opdivo), avelumab (Bavencio). The mTOR inhibitors include therapies such as everolimus (Afinitor), temsirolimus (Torisel). Often, immunotherapies will be used in combination with each other, or in combination with anti-VEGFR medications. The mTOR inhibitors are also utilized in combination with anti-VEGFR medications; however, use of two concomitant anti-VEGFR medications has not been evaluated, and given the unfavorable safety profiles of these medications, combination treatment is not advised.

III. As of March 2021, all three categories of medications are used for clear cell RCC. In the subsequent treatment setting, NCCN Cat. 1 recommended regimens include cabozantinib...
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.

IV. Treatment choice is based on stage of disease, prognosis, line of therapy, and other patient characteristics. Tolerability and safety considerations are taken into account for treatment choice as well. Given the extensive treatment options, combinations, and unfavorable safety profiles that require extensive medication monitoring, medication should be prescribed by or in consultation with a specialist.

V. In 2013 tivozanib (Fotivda) was evaluated in a Phase 3 trial vs. sorafenib (Nexavar) in 517 patients with RCC for initial targeted therapy in those that had received up to one prior systemic treatment. Patients had prior nephrectomy, clear cell RCC, and up to one prior therapy that was not an anti-VEGFR. Progression-free survival (PFS) was statistically significant favoring tivozanib (Fotivda); however, the overall survival (OS) was not statistically different. In 2013, the FDA issued a Complete Response Letter to Aveo, given an inconclusive risk benefit assessment and required another trial from the manufacturer in the advanced setting.

VI. Following the CRL, tivozanib (Fotivda) was evaluated in an open-label, randomized, Phase 3 trial vs. sorafenib (Nexavar) in 350 adults with RCC. Ninety-eight percent of patients had clear cell histology. Patients had advanced disease and were relapsed or refractory to two or three prior systemic therapies, including at least one anti-VEGFR therapy. Forty-five percent of patients had two prior anti-VEGFR therapies and 26% had prior checkpoint inhibitor therapy. About 60% of patients had intermediate, 20% had favorable, and 20% had poor prognoses. The study showed a statistical increase in PFS (5.6 months vs. 3.9 months), as well as partial responses (18% vs. 8%); however, OS was not statistically different and numerically favored sorafenib (Nexavar). To date, tivozanib (Fotivda) has not proven to have clinically meaningful outcomes such as increased survival, improvement in quality of life or symptom control. This is similar for the comparator, sorafenib (Nexavar). Thus, clinical benefit of either therapy remains unclear.

VII. To date, the safety tivozanib (Fotivda) is similar to other anti-VEGFR medications. Serious adverse events (AE) occurred in 11% of patients on tivozanib (Fotivda) and in 10% for sorafenib (Nexavar). AE more frequent with tivozanib (Fotivda): hypertension (44% vs. 31%), bleeding (17% vs. 12%), nausea (30% vs. 18%), decreased appetite (39% vs. 30%), dysphonia (27% vs. 9%), cough (22% vs. 15%), and hypothyroidism (24% vs. 11%). AE more frequent with sorafenib (Nexavar): diarrhea (54% vs. 44%), rash (52% vs. 18%), and palmar-plantar syndrome (41% vs. 16%). Stomatitis, vomiting, pain, dyspnea, and weight loss were common and occurred in similar rates between treatment arms.

VIII. Dose interruption due to AE occurred in 48% of the tivozanib (Fotivda) group and 63% of the sorafenib (Nexavar) group. Dose reductions due to AE occurred in 24% for tivozanib (Fotivda) and 38% for sorafenib (Nexavar). The lower dose reduction and interruption rates for tivozanib (Fotivda) are likely attributable to the seven-day break within each cycle vs. continuous dosing with sorafenib (Nexavar). Given lack of long-term safety evaluation and lack of evaluation against placebo, true benefits and harms are unknown at this time. At this time there is insufficient safety information (given limited patient experience and duration of therapy) to definitively indicate that there is substantial safety differences between any of the anti-VEGFR therapies.
Investigational or Not Medically Necessary Uses

I. Tivozanib (Fotivda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Renal cell carcinoma prior to third-line.
      i. Tivozanib (Fotivda) has been evaluated for first-line and second-line treatment but did not achieve FDA-approval given uncertain risks and benefits.
   B. The following indications have not been sufficiently studied for efficacy and use outside of clinical trials is not advised given the unfavorable safety profile alone or in combination with other medications:
      i. Renal cell carcinoma in combination with other oncolytic therapies
      ii. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
      iii. Prostate cancer
      iv. Breast cancer
      v. Ovarian, fallopian tube, or primary peritoneal cancer
      vi. Lung Cancer
      vii. Gastrointestinal tumors
      viii. Hepatocellular carcinoma
      ix. Cholangiocarcinoma
      x. Colorectal cancer
      xi. Glioblastoma

References


Policy Implementation/Update:

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<td>Policy created</td>
<td>05/2021</td>
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Policy Type: PA/SP Pharmacy Coverage Policy: UMP159

Tobramycin (TOBI®) inhalation solution, generic tobramycin inhalation solution, tobramycin (KITABISTM) inhalation solution, tobramycin (TOBI Podhaler®) inhalation solution and tobramycin (Bethkis®) inhalation solution are aminoglycoside antibacterial drugs that act primarily by disrupting protein synthesis in the bacterial cell which eventually leads to death of the cell. Tobramycin inhalation solutions have activity against a wide range of gram-negative bacteria including *Pseudomonas aeruginosa*.

**Length of Authorization**
- Initial: 12 months (7 fills per year)
- Renewal: 12 months (7 fills per year)

**Quantity limits**

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<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>tobramycin (TOBI)</td>
<td>300 mg/5mL one single-use ampule</td>
<td>Cystic fibrosis with <em>Pseudomonas aeruginosa</em></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>generic tobramycin</td>
<td>300 mg/5mL one single-use ampule</td>
<td></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>inhalation solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tobramycin (KITABIS)</td>
<td>300 mg/5mL one single-use ampule</td>
<td></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>tobramycin (Bethkis)</td>
<td>300 mg/4 mL one single-use ampule</td>
<td></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>tobramycin (TOBI Podhaler)</td>
<td>28mg inhalation capsule</td>
<td></td>
<td>224 inhalation capsules /28 days</td>
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**Initial Evaluation**

I. **Generic tobramycin inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Member is six years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. Member has tested positive for *Pseudomonas aeruginosa* in the lungs; **AND**
      2. Member has FEV₁ >25% or <80% ; **AND**
      3. Member is **not** colonized with *Burkholderia cepacia*

II. **Tobramycin (TOBI) inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**

*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.*
B. Treatment with generic tobramycin inhalation solution has been ineffective, contraindicated, or not tolerated.

III. Generic tobramycin inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (TOBI) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution are considered investigational when used for all other conditions, including but not limited to:
   A. Non–cystic fibrosis bronchiectasis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. The safety and efficacy of tobramycin inhalation solution in pediatric patients under six years of age has not been established due to the lack of clinical trial data. The use is not indicated in pediatric patients under the age of six.

II. Tobramycin inhalation solution is administered twice daily in alternating periods of 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next “28 days on/28 days off” cycle. To ensure appropriate dosing of tobramycin nebulizer or podhaler in members with cystic fibrosis, approval will allow for 7 fills within a 1-year approval period.

III. Safety and efficacy have not been demonstrated in patients with FEV1 <40% or >80% (Bethkis), FEV1 <25% or >80% (Tobi Podhaler), FEV1 <25% or >75% (Tobi and Kitabis), or patients colonized with Burkholderia cepacia.

IV. Tobramycin inhalation solution is used in treatment of cystic fibrosis and need to be prescribed by, or in consultation with, a pulmonologist because of the complexity of the disease state.

V. Guidelines developed by the Pulmonary Therapies Committee of the Cystic Fibrosis Foundation made the following recommendations for tobramycin solution for inhalation (TSI) (written prior to the approval of aztreonam lysine inhalation solution (AZLI)):
   • Moderate to severe lung disease (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is strongly recommended to improve lung function and reduce exacerbations (grade A recommendation).
   • Mild lung disease or asymptomatic (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is recommended to reduce exacerbations (grade B recommendation).

VI. In the absence of direct comparative trails there’s no evidence to conclude that one product is safer or more effective than another.

Investigational or Not Medically Necessary Uses

I. Non–cystic fibrosis bronchiectasis
A. Efficacy of adding inhaled tobramycin solution (TS) to oral ciprofloxacin was studied. In a multicenter trial, 53 patients with known P. aeruginosa infection who were having exacerbations of bronchiectasis were randomly assigned to receive ciprofloxacin plus inhaled TS or ciprofloxacin plus placebo for two weeks. The addition of inhaled TS to ciprofloxacin did not improve clinical outcomes compared to ciprofloxacin alone, although there was a marked reduction of Pseudomonas density in the sputum of patients who received inhaled TS plus ciprofloxacin. Wheezing was more common in the inhaled TS plus ciprofloxacin group. Based on current data, inhaled aerosols of antibiotics, such as TS, cannot be recommended alone or in combination with ciprofloxacin for acute exacerbations in bronchiectasis.

References

1. KITABIS PAK package insert. Catalent Pharma Solutions, LLC Woodstock, IL 60098. 12/06/2019
2. TOBIpodhaler package insert. Novartis Pharmaceuticals Corporation (10/02/2015)
3. TOBI inhalation solution package insert. Novartis Pharmaceuticals Corporation (10/05/2018)

Policy Implementation/Update:

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<td>Removed step through tobramycin (BETHKIS) inhalation solution and tobramycin (KITABIS) inhalation solution</td>
<td>12/2021</td>
</tr>
<tr>
<td>• Updated criteria to policy format</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Tobramycin (TOBI Podhaler) inhalation solution is considered medically necessary if treatment with tobramycin (KITABIS) inhalation solution and tobramycin (TOBI) inhalation solution has been ineffective, contraindicated, or not tolerated</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution are considered medically necessary if treatment with tobramycin (KITABIS) and generic tobramycin has been ineffective, contraindicated or not tolerated</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Added tobramycin (KITABIS) to policy</td>
<td>03/2013; 03/2017;</td>
</tr>
</tbody>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP068

Description
Tolvaptan (Jynarque) is a selective vasopressin V(2)-receptor antagonist.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tolvaptan (Jynarque)</td>
<td>15 mg tablets</td>
<td></td>
<td>28 tablets/28 days</td>
</tr>
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<td>30 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
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<td></td>
<td>15 &amp; 15 mg tablet therapy pack</td>
<td>Autosomal dominant polycystic kidney disease</td>
<td>56 tablets/28 days (1 box/28 day)</td>
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<td>30 &amp; 15 mg tablet therapy pack</td>
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<td>90 &amp; 30 mg tablet therapy pack</td>
<td></td>
<td>56 tablets/28 days (1 box/28 day)</td>
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Initial Evaluation

I. Tolvaptan (Jynarque) may be considered medically necessary when the following are met:
   A. Prescribed by prescribed by, or, in consultation with a nephrologist; AND
   B. A diagnosis of autosomal dominant polycystic kidney disease (ADPKD) when the following are met:
      1. Diagnosis is confirmed by imaging (e.g., ultrasound, CT, MRI) or genetic test; AND
      2. Member has rapidly-progressing ADPKD (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); AND
      3. Member does not have Stage 5 chronic kidney disease (CKD) defined as a glomerular filtration rate (GFR) < 15 mL/min/1.73 m2, or receiving dialysis

II. Tolvaptan (Jynarque) is considered investigational when used for all other conditions, including but not limited to:
    A. Hyponatremia
Renewal Evaluation

I. Member experienced disease stability, or improvement (e.g., reduction in number and/or rate of cyst production, change in renal function, reduction in rate of total kidney volume growth, slowed rate of kidney function decline); **AND**

II. Documented lack of unacceptable toxicity

Supporting Evidence

I. Polycystic kidney disease (PKD) includes inherited diseases that cause irreversible decline in kidney function. PKD may be inherited as an autosomal dominant or recessive trait. The autosomal dominant form (autosomal dominant PKD [ADPKD]) is the most common genetic cause of chronic kidney disease (CKD). The majority of individuals with PKD eventually require renal replacement therapy.

II. The diagnosis of ADPKD is most commonly made via screening using ultrasound, CT scan or MRI. Genetic testing is available for definitive diagnosis, but is rarely performed. Confirmed diagnosis of ADPKD via one of these tests is required prior to coverage of Jynarque.

III. Tolvaptan (Jynarque) was shown to slow the rate of decline in renal function in adults at risk of rapidly-progressing ADPKD in two phase 3 randomized controlled trials, TEMPO and REPRISE.

- **TEMPO**: Included 1445 adult patients with estimated creatinine clearance >60 mL/min and total kidney volume (TKV) >750 mL. The trial met the pre-specified primary endpoint of 3-year change in TKV (p<0.0001). The annual decline in eGFR was slower among patients who received tolvaptan compared to placebo (-2.72 versus -3.70 mL/min/1.73 m² per year). Tolvaptan also reduced the rate of decline in kidney function at three years (hazard ratio [HR] 0.39, 95% CI 0.26-0.57), and the incidence of clinically significant kidney pain (HR 0.64, 95% CI 0.47-0.89).

- **REPRISE**: Examined the effect of tolvaptan in patients with ADPKD who had reduced eGFR; such patients were generally not included in the TEMPO trial. At 12 months, the change from baseline eGFR was lower among those assigned tolvaptan as compared with placebo (-2.34 versus -3.61 mL/min/1.73 m²); the group difference was 1.27 mL/min/1.73 m² (95% CI 0.86-1.68).

- The analysis of the REPRISE trial, and a post-hoc analysis of the TEMPO trial, showed that tolvaptan (Jynarque) may extend the time until stage 5 CKD (ie, eGFR <15 mL/min/1.73 m²) from six to nine years among patients who start tolvaptan with an eGFR <60 mL/min/1.73 m², and, even longer among those who start tolvaptan earlier.

- Clinical trial criteria for rapidly progressive ADPKD
  i. Age 18-50 AND eGFR ≥60 mL/min/1.73 m² AND Total Kidney Volume ≥750 mL
  ii. Age 18-55 AND eGFR 25 to 65 mL/min/1.73 m²
  iii. Age 56-65 AND eGFR 25 to 44 mL/min/1.73 m² AND documented eGFR decline of more than 2.0 mL/min/1.73 m² per year

- The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m² or receiving dialysis).

IV. Tolvaptan (Jynarque) is a part of a Risk Evaluation and Mitigation Strategy (REMS) program to monitor for liver injury.

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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.

September 01, 2022
V. Tolvaptan (Jynarque) should not be used off-label for other diagnoses due to lack of evidence, and risk of adverse events.

VI. In clinical trials, outcomes included the reduction in rate of total kidney volume growth, the slowed rate of kidney function decline, improvement in renal function, a change in mean arterial blood pressure, and change in renal pain. Stability of disease, or improvement in at least one of these measures, is indicative of treatment response. Additionally, fatal liver injury is a significant safety concern of Jynarque; liver function tests should be monitored periodically.

**Investigational or Not Medically Necessary Uses**

I. Hyponatremia
   A. Samsca, is a tolvaptan formulation that is FDA approval for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium of less than 125 mEq/L or less marks hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Jynarque has not been evaluated for treatment of hyponatremia.

**References**

1. Jynarque [Prescribing Information]. Tokyo, Japan: Otsuka Pharmaceutical Co. April 2018
5. UpToDate, Inc. Treatment of autosomal dominant polycystic kidney disease. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated April 12, 2019

**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
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<td>Updated to policy format. Added the following: quantity limits for new 15 mg and 30 mg tablet, therapy to be prescribed by or in consultation with nephrologist, limited use to reflect patient population included in clinical trial (i.e. rapidly progressing ADPKD and do not have stage 5 CKD).</td>
<td>5/2019</td>
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<tr>
<td>Date created</td>
<td>05/2018</td>
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Policy Type: PA/SP

Policy: UMP099

Description
Tolvaptan (Samsca®) is an orally administered vasopressin V2-receptor antagonist which causes an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Length of Authorization
- Initial: one month
- Renewal: no renewal

Quantity limits

<table>
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<tr>
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<th>Dosage Form</th>
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</thead>
<tbody>
<tr>
<td>tolvaptan (Samsca)</td>
<td>15 mg tablet</td>
<td>Hypervolemic or euvolemic hyponatremia</td>
<td>30 tablets/30 days*</td>
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<tr>
<td></td>
<td>30 mg tablet</td>
<td></td>
<td>60 tablets/30 days*</td>
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</table>

*Therapy should not be continued past 30 days.

Initial Evaluation

I. Tolvaptan (Samsca) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist or nephrologist; **AND**
   C. Medication was initiated in the hospital; **AND**
   D. The requested treatment course will not exceed a 30-day duration per FDA recommendation; **AND**
   E. A diagnosis of **clinically significant hypervolemic or euvolemic hyponatremia** when the following are met:
      1. Serum sodium is less than 125 mEq/L; **OR**
      2. Serum sodium is greater than 125 mEq/L **and** patient has symptomatic hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion) that has resisted correction with fluid restriction

II. Tolvaptan (Samsca) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
   B. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms
Supporting Evidence

I. Per the label, tolvaptan (Samsca) is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

II. Safety and effectiveness of tolvaptan (Samsca) in pediatric patients has not been established.

III. Per the label, patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriplegia, seizures, coma and death.

IV. To minimize the risk of liver injury, tolvaptan (Samsca) should not be administered for more than 30 days. Based largely on the hepatic injury noted in the TEMPO trial, on April 2013 the FDA recommended that: “treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis”.

V. It has not been established that raising serum sodium with tolvaptan (Samsca) provides a symptomatic benefit to patients.

Investigational or Not Medically Necessary Uses

I. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
   A. Jynarque (tolvaptan) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD; however, the recommended dosing in Jynarque differs from the Samsca product. Per the tolvaptan (Samsca) label, because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS.

II. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms.
   A. Tolvaptan (Samsca) has not been studied in a setting of urgent need to raise serum sodium acutely.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Policy created</td>
<td>11/2019</td>
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Washington State Rx Services is administered by Moda Health

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.
Policy Type: PA/SP Pharmacy Coverage Policy: UMP247

Description
Tralokinumab (Adbry) is a subcutaneous fully human monoclonal antibody of interleukin-13 (IL-13).

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>tralokinumab (Adbry)</td>
<td>150 mg prefilled syringe</td>
<td>Moderate-to-Severe Atopic Dermatitis</td>
<td>First Month: 6 syringes/28 days</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 4 syringes/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg (2 syringes)/28 days may be considered for patients under 100 kg who achieve clear skin</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Tralokinumab (Adbry) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, a dermatologist or allergist; AND
   C. A diagnosis of moderate-to-severe atopic dermatitis when the following are met:
      1. Body surface area (BSA) involvement of at least 10%; OR
         i. Involves areas of the face, ears, hands, feet, or genitalia; AND
      2. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or ALL are contraindicated:
         i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
         ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
         iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); AND

II. Tralokinumab (Adbry) is considered investigational when used for all other conditions, including but not limited to:
   A. Asthma or COPD
   B. Nasal polyps

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.

September 01, 2022
C. Pediatric or adolescent atopic dermatitis  
D. Ulcerative colitis  
E. Alopecia areata

Renewal Evaluation

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

Supporting Evidence

I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.

II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age)

III. Treatment for moderate-to-severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between tralokinumab (Adbry) and other therapies. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age.

IV. Tralokinumab (Adbry) was evaluated in three randomized, double-blind, placebo-controlled, Phase III trials. Two as monotherapy (ECZTRA 1 and ECZTRA 2) and one in addition to topical corticosteroids (ECZTRA 3). Medication was administered as a 600 mg loading dose on day 0, followed by 300 mg every two weeks or placebo. In ECZTRA 1 and 2: at 16 weeks, responders continued on and were re-randomized to continue 300 mg every two weeks, change to 300 mg every four weeks, or placebo. In ECZTRA 3: at 16 weeks responders were re-randomized to tralokinumab (Adbry) every two or four weeks. All patients included in the trials were adults,
and safety and efficacy in adolescent and pediatric patients is unknown. Patients included in the trials had moderate-to-severe AD (IGA 3-4) with BSA of at least 10% and had insufficient response to topical therapies. The majority had utilized several topical therapies, systemic immunosuppressants and phototherapy. Patients in ECZTRA 3 (6%) had history of use of dupilumab (Dupixent), and patients in ECZTRA 1 and 2 did not have a history of use.

V. Tralokinumab (Adbry) showed positive outcomes in all three trials with regard to morbidity, symptom control, and quality of life parameters via proportion of patients with an IGA of 0 or 1, proportion of patients meeting EASI 75, SCORAD change, change in NRS score from baseline, DLQI, and in ECZTRA 3 – TCS utilization - further details on measurement tools are provided in the appendix below.

VI. ECZTRA 1 and 2: When responders of therapy were re-randomized to tralokinumab (Adbry) every two weeks, every four weeks, or placebo, the majority of patients on every two-week therapy maintained response, while there was a nonsignificant difference in response maintained between the every-two-week and placebo arms for maintenance in ECZTRA 1. This was attributed to patients being counted as non responders if any other therapy (e.g., TCS) was utilized. Additionally, many of those that were transitioned to placebo maintained response out to week 52. There was a difference seen in maintenance of response in ECZTRA 2 vs. placebo.

VII. ECZTRA 3: Those that did not achieve the endpoints at week 16 were allowed to continue therapy, of those patients, 30.5% met IGA 0/1 and 55.8% met EASI 75 at week 32. Additionally, after re-randomization to tralokinumab (Adbry) every two weeks or every four weeks, 90% and 78% of patients maintained IGA 0/1, respectively, and 92.2% and 90.8% of patients maintained EASI 75, respectively.

VIII. The overall incidence of adverse events (AE) was similar to placebo in clinical trials. Common AE (>5%): AD, URTI, skin infection, pruritus, headache, and conjunctivitis. Eye disorders are notable AE for tralokinumab (Adbry) as there was more URI (up to 3% greater) and conjunctivitis (up to 5% greater) seen in tralokinumab (Adbry) then in placebo. In addition, there were also eight cases of keratoconjunctivitis and keratitis compared to the one case seen on placebo. These AE’s are seen similarly for dupilumab (Dupixent). Skin infections overall, as well as those that required systemic treatment, were greater in the placebo group. A long-term extension trial evaluating safety (EZTEND) is expected to be complete in September 2021.

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 therapies be based on cost-effectiveness.

Investigational or Not Medically Necessary Uses

I. Tralokinumab (Adbry) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Asthma or COPD
   B. Nasal polyps
   C. Pediatric or adolescent atopic dermatitis
   D. Ulcerative colitis
   E. Alopecia areata

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.

September 01, 2022
Appendix

<table>
<thead>
<tr>
<th>Outcomes Key</th>
<th>Name</th>
<th>Explanation</th>
<th>Use and Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>IGA: Investigators Global Assessment Scale</strong></td>
<td>Five-point scale assesses AD severity: 0-4, 0 is clear and 4 is severe. Decrease in score indicates improvement of AD signs and symptoms.</td>
<td>-Used for clinical trials -Clinically important difference is a 1-point change</td>
</tr>
<tr>
<td></td>
<td><strong>EASI: Eczema Area and Severity Index</strong></td>
<td>Scale assesses severity and extent of AD, 0-72 points. EASI 75 = 75% improvement from baseline. Measures 4 characteristics: erythema, infiltration/papulation, excoriations, lichenification, each on a scale of 0-3. These have different weight for each of the four body regions and are summed.</td>
<td>-Used for clinical trials -Clinically important difference is a 7-point change</td>
</tr>
<tr>
<td></td>
<td><strong>SCORAD: Scoring Atopic Dermatitis</strong></td>
<td>Tool used to evaluate severity and extent of AD. Assesses 3 components: BSA, severity, and symptoms. Extent is assessed as a percentage of each defined body area and reported as a sum. Maximum score is 100% for extent. The severity of six symptoms is assessed using a four-point scale: erythema, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness. Severity has a maximum score of 18 points. Symptoms are recorded on a scale of 0-10, where 10 is the worst score imaginable. Entire score has a maximum of 103, higher scores=more severe condition.</td>
<td>-Used in clinical trials -Clinically important difference is a ~9 point change</td>
</tr>
<tr>
<td></td>
<td><strong>NRS: Pruritus Numerical Rating Scale</strong></td>
<td>Tool used by patients to report the intensity of their itch. A scale of 0-10: 10 being worst itch imaginable. Often measured as a weekly average of the peak daily pruritus, tracked throughout a trial.</td>
<td>-Used in clinical trials -Clinically important difference is 3-4 points</td>
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<td></td>
<td><strong>DLQI: Dermatology Life Quality Index</strong></td>
<td>Tool used widely in dermatology. 10 item questionnaire, assesses 6 aspects: feelings, activities, leisure, work/school performance, personal relationships, treatment. Max score per question is 3. DLQI is calculated by summing of scores for a maximum of 30. 0-1: no effect, 21-30: extremely large effect.</td>
<td>-Sometimes used in practice. -Clinically important difference is 2-7-point change</td>
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References


Policy Implementation/Update:

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<th>Date</th>
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<tr>
<td>Policy update to prefer Dupixent</td>
<td>05/2021</td>
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<tr>
<td>Policy created</td>
<td>02/2021</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP100

Description
Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and MEK1 and MEK2 activity; while also, inhibiting BRAF V600 mutation-positive melanoma cell growth. Dabrafenib (Tafinlar) is an orally administered BRAF V600 inhibitor. When used in combination, there is greater and prolonged inhibition compared to either drug alone.

Length of Authorization
- Initial: Six months
- Renewal:
  - Six months for adjuvant treatment of melanoma that had lymph node involvement and was completely resected. One time renewal only (i.e., one total year of therapy authorized).
  - 12 months for all other indications

Quantity limits

<table>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
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<td>trametinib</td>
<td>0.5 mg tablet</td>
<td>Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy</td>
<td>90 tablets/30 days</td>
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<td>(Mekinist)</td>
<td>2 mg tablet</td>
<td>Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy</td>
<td>30 tablets/30 days</td>
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<td>50 mg capsule</td>
<td>Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy</td>
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<tr>
<td>dabrafenib</td>
<td>75 mg capsule</td>
<td>Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients</td>
<td>120 capsules/30 days</td>
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<tr>
<td>(Tafinlar)</td>
<td></td>
<td>Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy</td>
<td></td>
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</tbody>
</table>
Initial Evaluation

I. Trametinib (Mekinist) and dabrafenib (Tafinlar) may be considered medically necessary in combination when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with an oncologist; **AND**
   C. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination **AND** no other oncolytic medication will be used concurrently; **AND**
   D. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
   E. A diagnosis of one of the following:
      1. **Anaplastic thyroid carcinoma; AND**
         a. The disease has been tested and shown to have BRAF V600E mutation; **AND**
         b. The disease is metastatic (stage IV); **OR**
      2. **Melanoma; AND**
         i. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
         ii. Melanoma is advanced (stage III), metastatic (stage IV), or unresectable; **OR**
            a. Melanoma has lymph node involvement and will be used as adjuvant treatment after complete resection; **OR**
      3. **Non-small cell lung cancer; AND**
         i. The disease has been tested and shown to have V600E mutation.

II. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Treatment after prior BRAF inhibitor therapy

III. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Colorectal cancer
   B. Ameloblastoma
   C. Thyroid cancer
   D. Erdheim Chester Disease
   E. Lung cancer
   F. CNS, and head and neck cancers, neurofibromas
   G. Rectal cancer
   H. Hepatoacellular cancer

*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.*

September 01, 2022
I. Leukemias, lymphomas
J. Prostate cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; AND
II. The medication is prescribed by or in consultation with an oncologist; AND
III. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; AND
IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease or decrease in size of tumor or tumor spread

Supporting Evidence

I. Dabrafenib (Tafinlar) plus trametinib (Mekinist) have been evaluated in several clinical trials in adults. Safety and efficacy in pediatrics have not been established.

II. Trials:
   ● The METRIC study evaluated trametinib (Mekinist) as monotherapy in V600E or V600K mutation-positive, unresectable or metastatic melanoma. It was an open-label trial against chemotherapy (dacarbazine or paclitaxel). The primary outcome was progression-free survival (PFS), and statistically favored trametinib (Mekinist).
   ● The COMBI-d study was a double-blind, active controlled trial of dabrafenib (Tafinlar) plus trametinib (Mekinist) versus dabrafenib (Mekinist) alone. Subjects included had unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Combination therapy was statistically favorable in PFS and overall-survival (OS).
   ● The COMBI-AD trial evaluated dabrafenib (Tafinlar) with trametinib (Mekinist) versus placebo in those with stage III melanoma with BRAF V600E or V600K mutations. Results statistically favored dabrafenib (Tafinlar) plus trametinib (Mekinist) compared to placebo.
   ● A study of dabrafenib (Tafinlar) alone or administered with trametinib (Mekinist) was evaluated in an open-label, Phase 2 trial in subjects with BRAF V600E mutation-positive NSCLC. Combination therapy was statistically favored in overall response rate (ORR) and duration of response (DOR).
   ● A study of dabrafenib (Tafinlar) administered with trametinib (Mekinist) evaluated subjects with thyroid cancer that were BRAF V600E mutation positive. The open-label, single-arm trial included those that were locally advance, unresectable or metastatic with no locoregional treatment options. Primary outcomes were ORR and DOR.
   ● Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.
   ● Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.
• Dabrafenib (Tafinlar) was evaluated in the BREAK-MD study as a single-arm, Phase 2, open-label trial for mutation-positive melanoma, metastatic to the brain. The primary outcomes were ORR and DOR.
• The COMBI-d study evaluated dabrafenib (Tafinlar) to trametinib (Mekinist) plus dabrafenib (Tafinlar) in first-line therapy for unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Overall survival was statistically in favor of combination therapy.
• The COMBI-v study evaluated dabrafenib (Tafinlar) plus trametinib (Mekinist) versus vemurafenib (Zelboraf) for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, and overall survival data was statistically in favor of dabrafenib (Tafinlar) plus trametinib (Mekinist).
• Adjuvant therapy for melanoma that had lymph node involvement and was completely resected, therapy is authorized for a total of one year maximum. Safety and efficacy beyond this time frame has not been sufficiently established.

III. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Treatment after previous BRAF inhibitor therapy
   A. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
II. Safety and efficacy of trametinib (Mekinist) and/or dabrafenib (Tafinlar) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Colorectal cancer
   B. Ameloblastoma
   C. Thyroid cancer
   D. Erdheim Chester Disease
   E. Lung cancer
   F. CNS, and head and neck cancers, neurofibromas
   G. Rectal cancer
   H. Hepatocellular cancer
   I. Leukemia, lymphoma
   J. Prostate cancer

References

Policy Implementation/Update:

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<thead>
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<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
</tr>
<tr>
<td>Criteria transitioned to policy, medications combined into one policy, addition of specialty prescriber, age edit, clarification on previous or alternative therapies to be considered for thyroid cancer. Quantity level limits updated.</td>
<td>11/2018</td>
</tr>
<tr>
<td>Criteria updated to include new indications of NSCLC and anaplastic thyroid cancer.</td>
<td>06/2018</td>
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<td>Previous Reviews</td>
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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.

September 01, 2022
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP142

Description
Trifluridine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation, and tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase. Together they make the product Lonsurf.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>trifluridine/tipiracil (Lonsurf)</td>
<td>15 mg – 6.14 mg tablets</td>
<td>Stomach or esophagogastric adenocarcinoma – metastatic, previously treated</td>
<td>80 tablets/28 days</td>
<td>189858</td>
</tr>
<tr>
<td></td>
<td>20 mg – 8.19 mg tablets</td>
<td>Colorectal cancer – metastatic, previously treated</td>
<td>80 tablets/30 days</td>
<td>189857</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Trifluridine/tipiracil (Lonsurf) may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by or in consultation with an oncologist or gastroenterologist; **AND**
   C. Trifluridine/tipiracil is used as monotherapy; **AND**
   D. A diagnosis of one of the following:
      1. **Colorectal cancer; AND**
         i. The disease is metastatic (i.e., stage IV); **AND**
         ii. The tumor has been tested and is documented to be KRAS mutant-type; **OR**
         iii. The tumor has been tested and is documented to be KRAS wild-type; **AND**
            a. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab); **AND**
iv. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), oxaliplatin and irinotecan-based chemotherapy; **AND**
v. The member has been previously treated with an anti-VEGF biological therapy (e.g., bevacizumab); **OR**

2. **Gastric or gastroesophageal junction adenocarcinoma; AND**
i. The disease is metastatic (i.e., stage IV); **AND**

ii. The member has been tested and has documentation of HER2/neu negative status; **OR**
   a. The member has been tested and has documentation of HER2/neu positive status; **AND**
   b. Has received prior HER2/neu targeted therapy (e.g., trastuzumab); **AND**

iii. The member has been previously treated with at least two prior lines of chemotherapy; **AND**

iv. Previous treatments included a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), a platinum therapy (e.g., cisplatin, carboplatin, oxaliplatin), and one of the following: a taxane (e.g., docetaxel, paclitaxel) or irinotecan

II. Trifluridine/tipiracil (Lonsurf) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Combination therapy with other oncolytic agents.
   B. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy.
   C. Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m2 orally twice daily.
   D. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type).
   E. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following — taxane or irinotecan.
   F. Biliary track cancers.
   G. Tumors that are not colorectal, gastric or gastroesophageal in nature.

**Renewal Evaluation**

I. The medication is prescribed by or in consultation with an oncologist or gastroenterologist; **AND**

II. Trifluridine/tipiracil (Lonsurf) continues to be used as monotherapy; **AND**

III. Body surface area is provided in meters squared; **AND**

IV. Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m2; **AND**

V. The member is not experiencing unacceptable toxicity from the therapy; **AND**

VI. The patient has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); **OR**
VII. Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued in the setting of progression.

Supporting Evidence

I. There is lack of safety and efficacy data from clinical trials for use in pediatric patients. This medication has not been evaluated outside of the adult population.

II. Pivotal clinical trials for FDA-approved indications evaluated safety and efficacy of trifluridine/tipiracil (Lonsurf) as monotherapy in heavily pretreated patients. The therapies listed in the above criteria had been tried and failed by the majority of patients enrolled in the clinical trials.

III. There is no globally accepted standard for first-line treatment of HER2/neu negative gastric or gastroesophageal adenocarcinoma. When these indications were added to the policy, NCCN guidelines were not updated to provide recommendations for this agent. Clinical trial experience with extensive patient treatment history is the basis for addition into the policy. Overall survival data in the third line treatment setting was shown to be 5.7 months for trifluridine/tipiracil (Lonsurf) vs 3.6 months for placebo.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have inconclusive evidence regarding safety and efficacy for use of trifluridine/tipiracil (Lonsurf).

I. Combination therapy with other oncolytic agents.

II. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy.

III. Colorectal, gastric, or gastroesophageal cancer at a dose < 20 mg/m2 orally twice daily.

IV. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type).

V. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan.

VI. Biliary track cancers.

VII. Tumors that are not colorectal, gastric or gastroesophageal in nature.

References


**Policy Implementation/Update:**

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<th>Date Created</th>
<th>May 2015</th>
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<tr>
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<td>May 2015</td>
</tr>
<tr>
<td>Last Updated</td>
<td>September 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>09/05/2019</td>
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</table>

**Action and Summary of Changes**

| Added new indication of stomach and esophagogastric adenocarcinoma based on clinical trial data that demonstrated overall survival in the third line treatment setting. | 03/2019 |
Policy Type: PA/SP          Pharmacy Coverage Policy: UMP210

Description
Triheptanoin (Dojolvi™) is a medium-chain triglyceride oral solution that provides a source of calories and fatty acids to bypass the long-chain enzyme deficiencies.

Length of Authorization
• Initial: Four months
• Renewal: 12 months

Quantity Limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>triheptanoin</td>
<td>8.3kcal/mL oral solution</td>
<td>Fatty acid oxidation disorders (LC-FAOD)</td>
<td>Monthly quantity to allow for a maximum of 35% of prescribed daily caloric intake</td>
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</tbody>
</table>

Initial Evaluation
I. Triheptanoin (Dojolvi™) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with molecularly confirmed LC-FAOD by a specialist in genetic metabolic disorders; **AND**
   B. Member does not have pancreatic insufficiency; **AND**
   C. Member has a history of hypoglycemia or cardiomyopathy or at least one episode of rhabdomyolysis; **AND**
   D. Member has at least TWO of the following diagnostic criteria:
      1. One or more known gene mutations in: CPT2, ACADVL, HADHA, or HADHB; **OR**
      2. Disease specific elevation of acylcarnitines on a newborn blood spot or in plasma; **OR**
      3. Low enzyme activity in cultured fibroblasts; **AND**
   E. Documentation of prescribed daily caloric intake is provided; **AND**
   F. Provider attests that the member is utilizing dietary management (e.g. low fat, high carbohydrate diet, avoidance of fasting); **AND**
   G. Provider attests that treatment with over the counter MCT oil has been ineffective, contraindicated, or not tolerated.

II. Triheptanoin (Dojolvi™) is considered investigational when used for all other conditions, including but not limited to:
   A. Pancreatic insufficiency
B. Fat malabsorption  
C. Impaired chylomicron transport  
D. Severe hyperchylomicronemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Prescriber attestation that the member has exhibited stability or improvement in disease activity [e.g., exercise tolerance, increased cardiac function tests]

Supporting Evidence

I. Per National Organization for Rare Disorders (NORD), disease state management of LC-FAOD is directed toward preventing and controlling acute episodes, which include symptoms such as hypoglycemia, rhabdomyolysis, and cardiac complications. Management often involves avoidance of fasting, maintaining low-fat, high-carbohydrate diet, and using low-fat nutritional supplements and MCT oil available over the counter (OTC).
II. Clinical presentation and the age of onset of LC-FAOD is variable. Signs and symptoms can be present at birth or develop later in adulthood. Even with treatment, many patients continue to experience symptom recurrence of variable frequency and severity. Hypoglycemia and cardiomyopathy typically occur at an earlier stage in life, rhabdomyolysis is usually present in asymptomatic patients later in adulthood. In addition to these three primary clinical manifestations, other symptoms are possible and include encephalopathy, peripheral neuropathy, and pigmentary retinopathy.
III. The effectiveness of triheptanoin (Dojolvi) has been established based on one phase 2, randomized, double-blind trial comparing triheptanoin (Dojolvi) with trioctanoin in 32 adult and pediatric patients (aged 7 years and older). Patients had a confirmed diagnosis of LC-FAOD, evidence of at least one significant episode of rhabdomyolysis, and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in CPT2, ACADVL, HADHA, HADHB.
IV. The primary efficacy outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Statistically significant outcomes were positive changes in left ventricular function and maximal heart rate reduction during an exercise tolerance test in the triheptanoin (Dojolvi) arm versus the trioctanoate arm.
V. The quality of the evidence was considered low because the study had a small sample size and had incomplete blinding. Moreover, there were applicability issues as some primary endpoints (cardiac function and exercise tolerance) were not clinically significant.
VI. Triheptanoin (Dojolvi) has not been directly compared to OTC MCT oil; therefore, there is insufficient evidence to conclude that triheptanoin (Dojolvi) is safer or more effective than OTC MCT oil.
VII. The most commonly reported adverse reactions for triheptanoin (Dojolvi) include gastrointestinal upset, musculoskeletal pain, fatigue, and headache.

VIII. There are no specific contraindications to using triheptanoin (Dojolvi), however, warnings include not using triheptanoin (Dojolvi) with feeding tubes manufactured of polyvinyl chloride (PVC) and avoiding use in patients with pancreatic insufficiency.

IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using triheptanoin (Dojolvi) for indications other than LC-FAOD.

Investigational or Not Medically Necessary Uses

I. Triheptanoin (Dojolvi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Pancreatic insufficiency
   B. Fat malabsorption
   C. Impaired chylomicron transport
   D. Severe hyperchylomicronemia

Appendix

The recommended target daily dosage of triheptanoin (Dojolvi) is up to 35% of the patient’s total prescribed daily caloric intake (DCI) divided into at least four doses and administered with mealtimes or with snacks.

I. Table 1: Dosage initiation and titration

| For patients not currently taking MCT product | • Initiate at total daily dosage of 10% DCI divided into four times per day.  
| For patients switching from another MCT product | • Increase recommended daily dose of up to 35% DCI over a period of two to three weeks.  |
| For patients switching from another MCT product | • Discontinue use of MCT products before starting triheptanoin (Dojolvi).  
| For patients switching from another MCT product | • Initiate triheptanoin (Dojolvi) at the last tolerated daily dose of MCT divided into four times per day.  
| | • Increase the total daily dose by approximately 5% DCI every two to three days until target dose of up to 35% DCI is achieved.  |

II. The quantity limit is to be determined based on the member’s prescribed daily caloric intake (DCI). Maximum total daily dose may not exceed 35% DCI. Round the total daily dosage to the nearest whole number.

\[ \text{Total Daily Dose (mL)} = \frac{\text{Member's DCI (kcal)} \times \text{Target (\% dose of DCI)}}{8.3 \text{ kcal/ml}} \]
References


Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Policy created</td>
<td>11/2020</td>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP194

Split Fill Management*

Description
Tucatinib (Tukysa™) is an orally administered tyrosine kinase inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

<table>
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<tr>
<th>Product Name</th>
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<th>Quantity Limit</th>
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<tbody>
<tr>
<td>tucatinib (Tukysa)</td>
<td>50 mg tablets</td>
<td>Metastatic breast cancer</td>
<td>60 tablets/30 days</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
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<td>120 tablets/30 days</td>
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Initial Evaluation

I. Tucatinib (Tukysa™) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The member has not previously progressed on or after treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], neratinib [Nerlynx]); **AND**
   D. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. Documentation is provided showing the disease is HER2-positive; **AND**
      2. Will be used in combination with trastuzumab and capecitabine; **AND**
      3. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
      4. Member does not have brain metastases; **AND**
         i. Member has progressed on, has a contraindicated to, or did not tolerate treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1); **OR**
      5. Member has brain metastases; **AND**
         i. Member has received ≥1 prior anti-HER2-based regimens in the metastatic setting

I. Tucatinib (Tukysa™) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Colorectal cancer

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.
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. Will be used in combination with trastuzumab and capecitabine; **AND**

V. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**

VI. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Tucatinib (Tukysa) was studied in a phase 2, double blind, placebo controlled, randomized trial (HER2CLIMB) in 612 patients with HER2-positive metastatic breast cancer with, or without, brain metastases who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1). The trial evaluated treatment with tucatinib (Tukysa) in combination with trastuzumab and capecitabine versus placebo, trastuzumab, and capecitabine. Patients in the trial had a median of 4 previous lines of therapy and 48% of patients had brain metastases. Overall survival at 2 years was 44.9% with the tucatinib (Tukysa) combination and 26.6% with trastuzumab, capecitabine, and placebo combination (hazard ratio for death, 0.66; 95% CI, 0.50-0.88; P = 0.005). Median overall survival was 21.9 months (tucatinib (Tukysa) combination) and 17.4 months (placebo, trastuzumab, and capecitabine). Secondary outcome of progression free survival at 1 year in patients with brain metastases was 24.9% with the tucatinib (Tukysa) combination and 0% with trastuzumab, capecitabine, and placebo combination (hazard ratio, 0.48; 95% CI, 0.34-0.69; P < 0.001).

II. Patients in the HER2CLIMB trial were excluded if they were previously treated with neratinib, afatinib, or any HER2 tyrosine kinase inhibitor at any time previously. Those who were treated with lapatinib more than 12 months from the start of the study were allowed to enroll in the trial; however, this accounted for only 6% of patients in the HER2CLIMB trial. At this time, there is lack of scientific evaluation for safety and efficacy of tucatinib (Tukysa) following progression on or after another tyrosine kinase inhibitor.

III. Although patients in the trial were heavily pretreated having failed trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1), FDA approval was granted in adults with or without brain metastases who have received ≥1 prior anti-HER2-based regimens in the metastatic setting. Agents such as TDM-1 and other oral tyrosine kinase inhibitors (i.e., neratinib, lapatinib) also have FDA approval and overall survival data in the previously treated metastatic setting. No head to head trials are available comparing tucatinib (Tukysa) to other tyrosine kinase inhibitors in this space.

IV. Given the population included in the HER2CLIMB trial consisted of heavily pretreated patients, criteria for coverage is set to reflect this patient population. Patients with CNS metastases, however, require only ≥1 prior anti-HER2-based regimen given limited treatment options and lack of strong data with other therapies in this population.
Investigational or Not Medically Necessary Uses

I. Tucatinib (Tukysa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Colorectal cancer
      i. As of June 2020, a phase 2 trial (MOUNTAINEER) was still recruiting to evaluate use of tucatinib plus trastuzumab in patients with HER2 positive colorectal cancer. Estimated study completion is anticipated December 31, 2021.

* 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

8. UpToDate, Inc. Lapatinib: Drug information. UpToDate [database online]. Waltham, MA. Available at: http://www.uptodate.com/home/index.htm

Policy Implementation/Update:

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September 01, 2022
Urea Cycle Disorder
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP034

Description
Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl) are orally administered nitrogen-binding agents used in the treatment of urea cycle disorder (UCD).

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

<table>
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<th>Quantity Limit</th>
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<tbody>
<tr>
<td>glycerol phenylbutyrate (Ravicti)</td>
<td>1.1g/mL (25mL bottle)</td>
<td>Urea Cycle Disorder</td>
<td>500mL (20 bottles)/30 days*</td>
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<td>sodium phenylbutyrate (Buphenyl)</td>
<td>500mg tablets</td>
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<td>1200 tablets/30 days</td>
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<td></td>
<td>3 GM/tsp powder</td>
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<td>500 GM (2 bottles)/28days**</td>
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*Max dose of 17.5ml/day (19g)
**Max Dose of 20g/day

Initial Evaluation

I. **Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl)** may be considered medically necessary when the following criteria below are met:
   A. Member is two months of age or older; **OR**
   B. If the request is for sodium phenylbutyrate (Buphenyl) tablet, member weighs at least 20 kg (44 lbs); **AND**
   C. A diagnosis of **Urea Cycle Disorder (UCD)** when the following are met:
      1. Management by dietary protein restriction and amino acid supplementation alone has been ineffective; **AND**
      2. Member will be continuing dietary protein restriction and, if needed, amino acid supplementation; **AND**
      3. Member has a plasma ammonia level greater than (>100 µmol/L; **AND**
      4. The request is for generic sodium phenylbutyrate; **OR**
         i. The request is for brand Ravicti OR brand Buphenyl, and treatment with generic sodium phenylbutyrate has been ineffective, contraindicated, or not tolerated

II. **Sodium phenylbutyrate (Buphenyl)** is considered **investigational** when used for all other conditions, including but not limited to:
A. Amyotrophic lateral sclerosis (ALS)
B. Acute hyperammonemia

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 a reduction from baseline in plasma ammonia levels; OR
   A. Member has maintained a plasma ammonia level within normal range for member’s age (see supporting evidence for normal ranges)

Supporting Evidence

I. Glycerol phenylbutyrate (Ravicti, GPB) and sodium phenylbutyrate (Buphenyl, SPB) are nitrogen-binding agents used in the chronic management of patients with urea cycle disorder (UCD) that cannot be managed by dietary protein restriction and/or dietary supplementation alone. UCD’s are rare genetic metabolic deficiencies caused by missing enzymes in the urea cycle, the most common being ornithine transcarbamylase [OTC] deficiency. All of the following are known UCDs: carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetyl glutamate synthetase [NAGS]. In UCD, the body is unable to convert the excess amino acids from food breakdown into uric acid that is secreted from the body resulting in high levels of ammonia in the body.

II. Diagnosis is based on clinical suspicion and biochemical and genetic testing. An elevated plasma ammonia level of 150 µmol/L (>260 µg/dl), or higher, in neonates and > 100 µmol/l (175 µg/dl) in older children and adults, is a strong indication for the presence of a urea cycle disorder. Genetic testing is available to assess for any of the enzymatic deficiencies noted above.

III. The goal of long-term management of UCD is to prevent hyperammonemia and includes dietary restrictions of protein, use of specialized formulas (in infants and young children), and oral nitrogen-scavenging agents. Hyperammonemia can be the first symptom in patients without a known family history of UCD or without knowing the patient’s genetics. Per Orphanet Guidelines for Rare Diseases, not all patients who recover from an episode of hyperammonemia require chronic nitrogen-scavenging agents, but they should be considered if the patient cannot manage the disease with dietary treatment alone. Additionally, as neither glycerol phenylbutyrate (Ravicti, GPB) or sodium phenylbutyrate (Buphenyl, SPB), which are only available as oral treatments, are approved for acute hyperammonemia, treatment in that condition should include stopping protein intake, hydration, and if required, IV use of sodium benzoate/sodium phenylacetate (Ammonul).

IV. The two notable differences between SPB and GPB is the unpleasant smell/taste and the higher than the recommended daily allowance of sodium in SPB. However, SPB has more real-world
data due to the time on the market as SPB was approved in 1996 and GPB was not approved until 2013. There have been several head-to-head non-inferiority studies in both adults and pediatrics, that showed GPB is as effective as SPB in treating UCD and has a slightly improved tolerability overall. Although, as there is more data in the use of SPB and because it is specifically indicated in OTC therapy, which is the most common UCD, SPB is typically started if UCD is suspected, and a genetic profile has not yet been completed. Additionally, in the absence of a clinically significant difference in efficacy between SPB and GPB, SPB is chosen as the preferred agent in the setting of UCD due to generic availability and a larger pool of safety and efficacy data.

V. Clinical study results showed ammonia values ranged from 9-35 µmol/L; however, the US UCD management guidelines do not specify a direct chronic ammonia treatment target number. Additionally, the normal value changes from neonates, to pediatrics, to adults and the consensus would be to focus on keeping the body within the normal range for the patient’s age on the lab test used, see below table.

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Normal Ammonia Range</th>
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</thead>
<tbody>
<tr>
<td>Adults</td>
<td>7-35 mmol/L</td>
</tr>
<tr>
<td>Children</td>
<td>28-57 mmol/L</td>
</tr>
<tr>
<td>Newborns</td>
<td>64-107 mmol/L</td>
</tr>
</tbody>
</table>

VI. The quantity limits noted in the table above reflect the maximum daily dose for each agent as there have not been safety/efficacy data over these doses. If the patient is moving from SPB to GPB a slight initial dosage change to ensure the patient is receiving the same amount of phenylbutyric acid, is required.

Investigational or Not Medically Necessary Uses

I. Amyotrophic Lateral Sclerosis (ALS)

A. In a phase 2 clinical study (CENTAUR), 137 patients with ALS were randomized 2:1 to receive sodium phenylbutyrate combined with taurursodiol (PB-TURSO) [N=89] or placebo [N=48], for 6 months. The primary endpoint was the ability to slow the disease progression as measured by changes in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The ALSFRS-R is the principal functional end point referenced in the latest FDA guidance for ALS trials and has shown to correlate with survival as well as quality of life, with each point decrease representing lost capability. The primary endpoint was the only endpoint to reach statistical significance with a p-value of 0.03 and a mean rate of change in the ALSFRS-R scores of -1.24 points per month for PB-TURSO versus -1.66 points in placebo. With an absolute mean difference at week 24 of 2.32 in PB-TURSO versus placebo.

B. An open-label extension (OLE) was allowed for those who completed the CENTAUR trial (97 patients in total between both arms) with the same end points to assess long term safety data. 56 patients remained on PB-TURSO and 34 remained on placebo. Note, this trial is still ongoing as of the policy date (12/2021) at 35 weeks after CENTAUR completion, and preliminary data noted risk of death was 44% lower in those on PB-TURSO versus placebo. With median survival duration of 25.0 months on PB-TURSO and...
18.5 months in placebo, a 6.5-month difference. The discussion by the authors noted that this OLE data with the CENTAUR data favored efficacy in quality of life and extension of life.

C. Only the primary endpoint of changes in the ALSFRS-R total score met statistical significance when comparing the placebo and the SPB-TURSO arms; this was reported in the value of the estimated mean change of the ALSFRS-R scale in each arm. Although the primary endpoint was met, patients in the treatment group experienced a mean ALSFRS-R score of -1.24. While this is marginally better than those receiving a those receiving placebo (-1.66), ALS guidelines indicate that a change of one or more can reflect large changes in quality of life. Since the patients experienced negative score reduction of greater than one, it is reasonable to say that this correlates with a clinically significant negative impact on quality of life. Additionally, the primary endpoint has not been substantiated by clinically meaningful data, including morbidity and mortality (e.g., time to death equivalent).

D. The use of SPB in ALS would join only two other FDA approved medications in the treatment of ALS. It is unknown where its place in therapy would be, as there is not sufficient data at this time showing definite measurable changes in SPB in slowing the disease progression or impacting quality of life. Currently, Riluzole is the only approved medication to improve survival and Edaravone has been shown to slow decline on the ALSFRS-R scores. These medications can be used together and routinely began early in therapy after initial diagnosis.

E. This was a phase II trial with the conclusion that more trials would be needed to explore this drug’s potential in ALS (there is currently a recruiting phase III-phoenix trial) and patients who completed this trial were allowed to stay on in an open-label extension which is still ongoing at the date of this policy’s creation. The use of sodium phenylbutyrate in this area is still experimental without quality data showing efficacy in the treatment of ALS.

References

2. Buphenyl [Prescribing Information]. Ucyckyd Pharma, Inc
**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated policy name, added second medication to the policy, sodium phenylbutyrate. Expanded on quantity limits to meet weight-based dosing; added clinical criteria for review of sodium phenylbutyrate. Updated renewal criteria. Added ALS as experimental indication. Revised and strengthened the supporting evidence.</td>
<td>12/2021</td>
</tr>
<tr>
<td>Criteria update: Included new FDA expanded indication for pediatric patients 2 months and older. Glycerol phenylbutyrate (Ravicti) was originally approved for pediatric patients 2 years and older. Additionally, a question was added to the renewal portion of this policy to assess for toxicity.</td>
<td>01/2019</td>
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<td>Previous Reviews</td>
<td>07/2013; 08/2013</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP216

Description
Uridine triacetate (Xuriden) is a pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA).

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>uridine triacetate (Xuriden)</td>
<td>2 g/packet</td>
<td>Hereditary orotic aciduria</td>
<td>240 g/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Uridine triacetate (Xuriden) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with hereditary orotic aciduria (HOA) by a provider specializing in the patient’s diagnosis or in consultation with a geneticist, hematologist or specialist in metabolic disorders; **AND**
   B. Member has at least **ONE** of the following diagnostic criteria:
      1. Molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene; **OR**
      2. Urine test indicating high levels of orotic acid and/or orotidine; **AND**
   C. Member has severe disease as defined by one or more of the following:
      1. Hematologic abnormalities (e.g. megaloblastic anemia, neutropenia, leukopenia); **OR**
      2. Renal tract obstruction (due to aggregation of orotic acid crystals); **OR**
      3. Immune dysfunction; **OR**
      4. Congenital anomalies; **OR**
      5. Physical and intellectual developmental delays; **AND**
   D. Provider attestation that member does not have ornithine transcarbamoylase (OTC) deficiency; **AND**
      1. Blood ammonia levels are within normal limits

II. Uridine triacetate (Xuriden) is considered investigative when used for all other conditions, including but **not** limited to:
   A. Fluoropyrimidine overdose/overexposure

*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.*
Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Prescriber attestation that the member has exhibited stability or improvement in disease symptoms [e.g., improvement in hematologic status, improvement in growth]

Supporting Evidence

I. HOA is an extremely rare genetic disorder affecting both men and women, with fewer than 25 cases of patients with this disorder worldwide have been reported in the medical literature. It is caused by variations in the uridine monophosphate synthase (UMPS) gene which is responsible for producing an enzyme that catalyzes the last two steps of the pyrimidine biosynthesis pathway. One of these two final steps is to convert orotic acid into another chemical substance. Because of the variation in the UMPS gene, individuals with this disorder have low levels of the enzyme needed to breakdown orotic acid and subsequently have a reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis.

II. The exact mechanism by which orotic acid buildup and uridine monophosphate synthase deficiency leads to signs and symptoms of the disease is not completely understood. Orotic acid is believed to improve the metabolism of folic acid and vitamin B12 and may play a role in gene transcription.

III. HOA is a clinically heterogenous disorder and individuals who retain some UMPS activity may be asymptomatic or only mildly affected. Features of more severe disease include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia, renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays.

IV. Diagnosis of HOA is confirmed by assessment of symptoms, family history, a urine test indicating high levels of orotic acid and/or orotidine, and a molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene. Not all patients will present with elevated orotic acid and/or orotidine urine levels; however, this is the most common laboratory abnormality seen in 80%-99% of patients. Deferential diagnosis of HOA includes urea cycle disorders one of which may also present with high blood levels of orotic acid, this disorder is known as ornithine transcarbamoylase (OTC) deficiency. OTC can be distinguished from HOA by evaluation of blood ammonia levels. Patients with HOA will have normal blood ammonia levels, whereas, patients with OTC deficiencies tend to have elevated ammonia levels.

V. Nucleotide replacement has been the mainstay of treatment of HOA. Case reports document rapid hematologic response with administration of uridine. Some patients treated with uridine have reached adulthood and some who have been treated with uridine lifelong have fathered or given birth to normal children. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.
VI. FDA approval of uridine triacetate (Xuriden) was based on collective evidence from case reports, pharmacokinetic studies, safety studies, and one Phase III, open-label, single-arm, six-week clinical trial and its six-month extension phase. The efficacy was evaluated in a Phase III trial which enrolled four patients with HOA (three male, one female; age range three to 19 years). Three patients were previously treated with uridine and were switched to uridine triacetate (Xuriden). One patient was treatment naïve. The study evaluated stability or improvement in patients’ hematologic parameters in the initial six-week period and the extension phase. By week six, three previously treated patients met the primary endpoint and maintained stability of their hematologic parameters, while one treatment naïve patient failed to meet the primary endpoint – improvement in hematologic parameters. The secondary endpoint was improved growth parameters (height and weight). Effect on growth was assessed in three patients and remained unchanged after 24 months of treatment.

VII. Uridine triacetate (Xuriden) is the only FDA approved therapy for HOA. The National Organization for Rare Disease Disorders and other expert opinions recommend treatment with uridine triacetate (Xuriden).

VIII. Uridine triacetate (Xuriden) should not be used for the treatment of fluoropyrimidine overdose/overexposure. A different formulation of uridine triacetate (Vistogard) has been approved by the FDA for the treatment of this condition.

Investigational or Not Medically Necessary Uses

I. Uridine triacetate (Xuriden) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fluoropyrimidine overdose/overexposure

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tr>
<td>Policy created</td>
<td>01/2021</td>
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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.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP223

Split Fill Management*

Description
Vandetanib (Caprelsa) is an orally administered kinase inhibitor, with activity at VEGF, EGFR, and RET kinases.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>vandetanib (Caprelsa)</td>
<td>100 mg tablets</td>
<td>Locally advanced or metastatic medullary thyroid cancer</td>
<td>60 tablets/30 days</td>
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<tr>
<td></td>
<td>300 mg tablets</td>
<td>Locally advanced or metastatic medullary thyroid cancer</td>
<td>30 tablets/30 days</td>
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</tbody>
</table>

Initial Evaluation

I. Vandetanib (Caprelsa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; AND
   C. A diagnosis of unresectable locally advanced or metastatic (stage III or IV) medullary thyroid cancer when the following is met:
      1. Medication is not used in combination with any other oncology therapy.

II. Vandetanib (Caprelsa) is considered investigational when used for all other conditions, including but not limited to:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung cancer

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.
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 on being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; AND
IV. Will not be used with any other oncology therapy; AND
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Vandetanib (Caprelsa) is a kinase inhibitor with activity at multiple kinases. In vitro studies show that vandetanib (Caprelsa) inhibits the activity of epidermal growth factor receptor (EGFR) family, vascular endothelial growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6, TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases. In mouse models, vandetanib (Caprelsa) reduced tumor cell growth and metastasis.

II. Vandetanib (Caprelsa) was studied in a Phase 3, double blind, placebo controlled, randomized trial (ZETA) in 331 patients with symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer. There is currently no evidence that it is safe and effective in treating other types of cancer.

III. The ZETA trial evaluated treatment with vandetanib (Caprelsa) as monotherapy versus placebo. Patients in the trial had either hereditary, sporadic, or unknown, or metastatic disease type. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Patients were excluded from treatment if they had significant cardiac, hematopoietic, hepatic, or renal dysfunction, were treated with chemotherapy and/or radiation therapy within four weeks of treatment with vandetanib (Caprelsa) or were taking any concomitant medications that may have affected QTc or induced CYP3A4 function.

IV. The primary endpoint evaluated in the ZETA trial was progression free survival (PFS). There was a statistically significant improvement in PFS for patients randomized to vandetanib (Caprelsa). The number of events in vandetanib (Caprelsa) arm was 59 (26%) and 41 (41%) in the placebo arm with a Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; p<0.001. The median survival in months for the placebo arm was 16.4 while for the vandetanib (Caprelsa) arm the median survival was not reached at the time of analysis;, however, the predicted median survival was 30.5 months. The mature data for overall survival (OS) was studied as a secondary endpoint and was similar between both treatment arms at 81.6 months for vandetanib (Caprelsa) and 80.4 months for placebo arm. However, OS survival data was not powered and was confounded by patients from the placebo arm that were eligible to start treatment with vandetanib (Caprelsa) after conclusion of the study. Other secondary endpoints evaluated included objective response rate (ORR) and disease control rate, both of which reached
statistical significance when compared to placebo. Quality of life and pain reduction outcomes were not reported or could not be evaluated.

V. Fifty-five percent (55%) of the patients on the vandetanib (Caprelsa) arm experienced grade 3 or 4 adverse events. Adverse reactions resulting in death occurred in five patients treated with vandetanib (Caprelsa) due to respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Causes of discontinuation in vandetanib (Caprelsa)-treated patients in >1 patient included asthenia, fatigue, rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine, and pyrexia. Serious adverse events in vandetanib (Caprelsa) treated patients in >2% of patients included diarrhea, pneumonia, and hypertension. Patients receiving vandetanib (Caprelsa) experienced a mean prolongation of their QT interval of 35ms, and sudden death and torsades des pointes have been observed with vandetanib (Caprelsa). A Risk Evaluation and Mitigation Strategy (REMS) is used to decrease the risk of these adverse events.

VI. Vandetanib (Caprelsa) has a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of recurrent or persistent medullary thyroid carcinoma and joins cabozantinib (Cabometyx) and selpercatinib (Retevmo) in the list of preferred systemic regimens. It is also recommended as the first line treatment option by the American Thyroid Association Guidelines. Vandetanib (Caprelsa) should be prescribed in consultation with, or by, an oncologist or endocrinologist for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib (Caprelsa) in patients with indolent, asymptomatic, or slowly progressive disease should only be considered after examining the treatment related risks of this agent.

Investigational or Not Medically Necessary Uses

I. Vandetanib (Caprelsa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung cancer

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Policy was updated and transitioned from an old criteria to a new format</td>
<td>02/2021</td>
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<tr>
<td>Removal of criteria requirements that are managed by provider (drug-drug interactions, REMS program, monitoring of CrCl, QT prolongation, hepatic impairments, hypertension, and other aspects from labeled warnings and precautions)</td>
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<td>Criteria created</td>
<td>02/2012</td>
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Policy Type: PA/SP
Pharmacy Coverage Policy: UMP071

Description
Venetoclax (Venclexta) is an orally administered B-cell lymphoma-2 (BCL-2) inhibitor.

Length of Authorization
- Initial:
  - Previously untreated CLL/SLL: 12 months
  - All other indications: Six months
- Renewal:
  - Previously untreated CLL/SLL: Cannot be renewed
  - All other indications: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>venetoclax (Venclexta)</td>
<td>Starter Pack</td>
<td>Chronic lymphocytic leukemia (CLL); Small lymphocytic lymphoma (SLL)</td>
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<td>10 mg tablets</td>
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<td>28 tablets/28 days</td>
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<td></td>
<td>100 mg tablets</td>
<td></td>
<td>120 tablets/30 days</td>
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<tr>
<td></td>
<td>100 mg tablets</td>
<td>Acute myeloid leukemia</td>
<td>180 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Venetoclax (Venclexta) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, an oncologist or hematologist; AND
   B. A diagnosis of:
      1. Relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND
         i. Received at least one prior therapy [e.g., Imbruvica (ibrutinib) or chemotherapy-containing regimen]; AND
         ii. Will be used as monotherapy or in combination with rituximab (Rituxan); OR
      2. Previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND
         i. Will be used in combination with obinutuzumab (Gazyva); OR
      3. Newly-diagnosed acute myeloid leukemia (AML); AND
         i. Age 75 years and older; OR
         ii. Have comorbidities that preclude use of intensive induction chemotherapy such as:
a. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3  
b. Severe cardiac or pulmonary comorbidity  
c. Moderate hepatic impairment  
d. CrCL ≥30 to <45 mL/min; AND

iii. Used in combination with azacitidine or decitabine or low-dose cytarabine

II. Venetoclax (Venclexta) is considered investigational for all other conditions, including but not limited to:
   A. Acute Myeloid Leukemia – Previously treated  
   B. Multiple Myeloma (MM)  
   C. Previously untreated CLL/SLL – Treatment for more than 12 months

Renewal Evaluation

I. Member has a diagnosis of relapsed/refractory CLL/SLL or newly diagnosed AML; AND
II. Clinical documentation of response to treatment, such as stabilization or improvement of disease; AND
III. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Venetoclax (Venclexta) is FDA-approved for the treatment of CLL/SLL, in adult patients with or without 17p deletion.
II. Patients included in venetoclax (Venclexta) monotherapy studies in CLL/SLL were relapsed/refractory to fludarabine-based regimens (e.g. Rituximab+Fludarabine+Cyclophosphamide, Fludarabine+Rituximab, Fludarabine+Cyclophosphamide) or alkylator-based regimens (e.g. chlorambucil, bendamustine), or to ibrutinib (Imbruvica) or idelalisib (Zydelig). Patients included in the venetoclax (Venclexta) plus rituximab (Rituxan) trial (MURANO) for relapsed CLL/SLL had received one to three previous treatments (including at least one chemotherapy-containing regimen). Prior radiation therapy or stem cell transplant alone is not considered a prior therapy as this treatment strategy alone was not considered an inclusion in pivotal trials.
III. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions. Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. The trial met its primary outcome of progression-free survival (PFS) in patients treated with Venclexta plus obinutuzumab compared to patients who received chlorambucil plus obinutuzumab, a commonly used standard of care. After a median follow-up of 28 months, Venclexta plus obinutuzumab reduced the risk of progression or death by 67% compared with chlorambucil plus obinutuzumab (hazard ratio: 0.33, 95%
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.

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IV. FDA granted accelerated approval to venetoclax (Venclexta) for use in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Initial FDA-approval was based on two phase Ib/II trials in this setting. The findings from these trials were consolidated by phase III confirmatory studies (VIALE-A and VIALE-C).

V. Venetoclax (Venclexta) was studied in a confirmatory phase III randomized (2:1) double-blind, placebo-controlled trial (VIALE-A), which assessed the efficacy and safety of venetoclax (Venclexta) in combination with azacitidine (IV or SQ administration) versus placebo+ azacitidine (n= 431). Participants in this trial had median age of 76 years, intermediate or poor/ high risk AML and at least one comorbidity precluding intensive therapies. At median duration of follow-up (20.5 months, <0.1- 30.7), median overall survival for venetoclax- azacitidine treatment arm was 14.7 months (95% CI; 11.9, 18.7) as compared to that of 9.6 months (95% CI; 7.4, 12.7) for placebo-azacitidine arm (HR 0.66; 95% CI; 0.52-0.85; p <0.0001). Additionally, treatment arm (venetoclax- azacitidine) also reported complete remission in 66.4% (95% CI; 60.6, 71.9) versus 28.3% (95% CI; 21.1, 36.3) in placebo-azacitidine arm (p<0.001) with 43.4% participants achieving complete remission before cycle 2.

VI. In VIALE-C clinical trial, efficacy and safety of venetoclax (Venclexta) in combination with low-dose cytarabine (LDAC) was compared with placebo plus LDAC in an ongoing double-blind, randomized (2:1) phase 3 study. From a pool of 211 randomized study participants (n=143 in treatment arm versus n= 68 in placebo arm), median follow-up of 17.5 months (95% CI; 0.1, 23.5) was reported at data cut-off. Median overall survival (OS) was 8.4 months in the treatment (venetoclax-cytarabine) arm versus 4.1 months in placebo-cytarabine arm (HR 0.70; 95% CI 0.50–0.99; P = 0.04). This OS data was not statistically significant. Additionally, a median event-free survival (EFS) was reported at 4.9 months vs 2.1 months for treatment and placebo arms, respectively (HR 0.61; 95% CI; 0.44, 0.84; P = 0.003).

Investigational or Not Medically Necessary Uses

I. Acute Myeloid Leukemia – Previously treated
   A. Pivotal trials leading to FDA approval were specifically in the previously untreated setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.

II. Multiple Myeloma (MM)
   A. Venetoclax (Venclexta) is currently being evaluated for use in MM and is the subject of ongoing clinical trials. As of March 2019, “FDA reviewed data from the BELLINI clinical trial (NCT02755597, Study M14-031) evaluating the use of Venetoclax (Venclexta) combined with bortezomib and dexamethasone in patients with multiple myeloma. The interim trial results demonstrated an increased risk of death for patients receiving Venetoclax (Venclexta) as compared to the control group. On March 6, 2019, the FDA required no new patients be enrolled on the Bellini trial. The FDA suspended enrollment in other ongoing multiple myeloma clinical trials of Venclexta.”
III. Previously untreated CLL/SLL – Treatment for more than 12 months

A. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb). Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. Treatment beyond 12 months has not been evaluated.

References

Policy Implementation/Update:

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<tr>
<td>Updated supporting evidence for venetoclax phase III confirmatory clinical trials for newly diagnosed acute myeloid leukemia (AML)</td>
<td>12/2020</td>
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<tr>
<td>Added new FDA approval in untreated CLL/SLL in combination with obinutuzumab (Gazyva)</td>
<td>06/2019</td>
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<tr>
<td>Added new FDA approval in Acute Myeloid Leukemia.</td>
<td>12/2018</td>
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<tr>
<td>Included new FDA expanded indication in CLL/SLL without 19p deletion and expanded initial approval to 6 months.</td>
<td>08/2018</td>
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Policy Type: PA

Pharmacy Coverage Policy: UMP224

Description
Vericiguat (Verquvo) is an orally administered guanylate cyclase stimulator.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>vericiguat (Verquvo)</td>
<td>2.5 mg tablets</td>
<td>Reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%</td>
<td>30 tablets/30 days</td>
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<td></td>
<td>5 mg tablets</td>
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<td></td>
<td>10 mg tablets</td>
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Initial Evaluation

I. Vericiguat (Verquvo) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, a cardiologist; AND
   C. A diagnosis of **chronic heart failure with reduced ejection fraction (HFrEF)** when the following are met:
      1. Member has HFrEF defined as New York Heart Association functional class II, III, or IV; AND
      2. Member has a documented reduced left ventricular ejection fraction of less than 45%; AND
      3. Provider attestation that member has recent evidence of worsening heart failure as defined by ONE of the following:
         i. Hospitalization for heart failure within the last six months; OR
         ii. Receiving intravenous (IV) diuretic therapy, within the last three months; AND
      4. Member is being treated with one agent from each of the following groups unless ineffective, contraindicated or not tolerated:
         i. Group 1: Beta-blocker (e.g., metoprolol succinate, carvedilol, bisoprolol)
ii. Group 2: ACE-I/ARB (e.g., lisinopril, losartan, valsartan, ramipril) OR ARNI (i.e. sacubitril/valsartan)

iii. Group 3: Mineralocorticoid antagonist (e.g., spironolactone)

II. Vericiguat (Verquvo) is considered investigational when used for all other conditions, including but not limited to:
   A. Heart failure with preserved ejection fraction (HfPfEF)

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND

III. Member has exhibited improvement or stability of disease symptoms; OR

IV. In the absence of improvement or stability of disease symptoms, the provider attests continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a Moda Health clinician.

Supporting Evidence

I. Vericiguat (Verquvo) was studied in one randomized, double-blind, placebo-controlled Phase 3 (VICTORIA) trial in 5,050 patients with chronic heart failure (NYHA functional class II, III or IV) with a reduced ejection fraction (<45%), evidence of recent decompensation or worsening heart failure, defined as recent hospitalization for heart failure in the last three months, hospitalization in the last three to six months, or receiving intravenous (IV) diuretic therapy, without hospitalization, within the last six months.

II. The primary efficacy outcome was a composite endpoint of death from cardiovascular causes or first hospitalization for heart failure. The primary endpoint was achieved by 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% CI 0.82 to 0.98; P=0.02).

III. Adverse events occurred in 80.5% of patients receiving vericiguat (Verquvo) with serious adverse events occurring in 32.8% of those patients. Notable side effects observed during the clinical trial include symptomatic hypotension (9.1% patients in vericiguat group vs. 7.9% in placebo group) and syncope (4.0% patients in vericiguat group vs. 3.5% in placebo group). Anemia developed in 7.6% patients in the vericiguat group compared to 5.7% patients in the placebo group. Of those developing anemia, 1.6% cases in the vericiguat group and 0.9% in the placebo group were considered serious adverse events.

IV. The 2017 AHA/ACC/HFSA guidelines recommend first-line therapy with an ACE-I or ARB and a guideline directed beta blocker (bisoprolol, carvedilol or metoprolol succinate) with use of diuretics as needed for symptom management. Spironolactone, sacubitril/valsartan, isosorbide

Washington State Rx Services is administered by Moda Health

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V. Vericiguat (Verquvo) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

Investigational or Not Medically Necessary Uses

1. Vericiguat (Verquvo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Heart failure with preserved ejection fraction (HFpEF)
      i. Vericiguat (Verquvo) was studied in two phase 2b trials, SOCRATES-PRESERVED and VITALITY-HFpEF, in the setting of chronic heart failure with preserved ejection fraction. The primary efficacy endpoints of change in baseline in log-transformed N-terminal pro-B-type natriuretic peptide (NT-ProBNP) and left atrial volume (LAV) and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) PLS quality index, respectively, were not met for either study and phase III studies were not pursued.

References


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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP072

Description
Vigabatrin’s (Sabril, Vigadrone) full mechanism of action is unknown at this time; however, it is an orally administered agent that has irreversible inhibition of gamma-aminobutyric acid transaminase (GABA-T).

Length of Authorization

- Initial: Three months for complex partial epileptic seizure, and one month for West Syndrome
- Renewal: 12 months

Quantity limits

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<tr>
<td>vigabatrin (Sabril)</td>
<td>500mg tablets</td>
<td>Refractory complex partial epileptic seizure, adjunct</td>
<td>180 tablets/30 days</td>
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<td>vigabatrin (Sabril,</td>
<td>500mg/packet powder for oral suspension</td>
<td>West Syndrome (infantile spasms)</td>
<td>120 packets/30 days</td>
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<td>Vigadrone)</td>
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Initial Evaluation

I. Vigabatrin (Sabril, Vigadrone) may be considered medically necessary when the following criteria below are met:

   A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   B. The member has had an ophthalmologic examination prior to initiating vigabatrin (Sabril) or will be examined no later than four weeks after initiation of therapy; **AND**
      1. The member will have an ophthalmologic examination at least every three months during treatment; **OR**
   C. The member is blind prior to initiation of therapy; **AND**
   D. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated; **AND**
   E. A diagnosis of one of the following:
      1. Complex partial epileptic seizure (focal onset impaired awareness seizure); **AND**
         i. Vigabatrin (Sabril, Vigadrone) will be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as...
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.

carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; AND

ii. A trial and failure of at least two anti-epileptic medications listed above; AND

iii. Member is two years of age or older; OR

2. West Syndrome (Infantile Spasms); AND

i. Member is between one month and two years of age; AND

ii. The prescribed dose does not exceed 150 mg/kg/day

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

A. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures
B. Tourette’s disorder
C. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)
D. Autoimmune encephalitis

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND

III. Provider attestation that ophthalmologic examination has been completed every three months since initiation of therapy; AND

IV. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided, regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated AND

V. A reduction in the severity or frequency of seizures or spasms; AND

A. Complex partial epileptic seizure (focal onset impaired awareness seizure); AND

1. The medication continues to be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; OR

B. West Syndrome (Infantile Spasms); AND

1. Clinical benefit has been assessed and documented within the first two to four weeks of treatment (please note: extensions will not be given if assessment has not taken place within four weeks of treatment initiation); AND

2. The prescribed dose does not exceed 150 mg/kg/day
Supporting Evidence

I. Vigabatrin (Sabril, Vigadrone) has a black box warning for permanent vision loss, and those who take the medication are at risk for vision loss with any amount of medication. The risk increases with greater doses and duration of vigabatrin (Sabril, Vigadrone) administration. This medication is available through a Risk Evaluation Mitigation Strategy (REMS) Program, and a specialist will need to be involved in prescribing to ascertain if the benefits of vigabatrin (Sabril, Vigadrone) outweigh the risk of vision loss.

II. Recommended ophthalmologic monitoring should start at baseline or within four weeks of initiating therapy, every three months during therapy, and through three to six months post discontinuation.

III. Vigabatrin (Sabril, Vigadrone) is FDA-approved for complex partial epileptic seizures (focal onset impaired awareness seizure) for ages two years and older and West Syndrome (infantile spasms) for ages one month to two years. In complex partial epileptic seizure, the medication is FDA-approved in the refractory setting after failure of other therapies and should be used in addition to at least one other anti-epileptic (i.e., vigabatrin [Sabril, Vigadrone] is an adjunct therapy).

IV. Vigabatrin (Vigadrone) is an AA-rated authorized generic of Sabril and is fully substitutable for both Sabril and generic vigabatrin 500mg/packet for oral solution.

V. The max dose of vigabatrin (Sabril, Vigadrone) is 3000 mg/day for complex partial epileptic seizure and a maximum of 150 mg/kg/day for West Syndrome.

VI. For West Syndrome, significant clinical benefit should be realized within four weeks of therapy initiation, and the medication should be discontinued if not. Due to the risks associated with the medication, continuation of therapy will not be granted in absence of clinical benefit.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy or have inconclusive evidence for use of vigabatrin (Sabril, Vigadrone).

I. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures

II. Tourette’s disorder

III. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)

IV. Autoimmune encephalitis

References


**Policy Implementation/Update:**

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<th>Date</th>
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<tr>
<td>• Updated minimum age for use as adjunct therapy for refractory complex seizures to age two and older to align with FDA-label age-expansion</td>
<td>03/2021</td>
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<td>• Added Vigadrone packets to policy</td>
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Date created:

| Date | 03/2019 |
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP198

Split Fill Management*

Description
Vismodegib (Erivedge) is an orally administered hedgehog pathway inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

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<th>Product Name</th>
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<tr>
<td>vismodegib (Erivedge)</td>
<td>150 mg capsules</td>
<td>Basal cell carcinoma; metastatic or locally advanced</td>
<td>28 capsules/28 days</td>
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Initial Evaluation

I. Vismodegib (Erivedge) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; AND
   C. Vismodegib (Erivedge) will NOT be used in combination with any other oncologic medication; AND
   D. Member has not progressed on any other oncologic medication (e.g. has not progressed on sonidegib [Odomzo]); AND
   E. A diagnosis of basal cell carcinoma (BCC) when the following are met:
      1. Member has metastatic (Stage IV) basal cell carcinoma; OR
      2. Member has locally advanced basal cell carcinoma; AND
         i. Basal cell carcinoma has recurred or progressed after radiation or surgery; OR
         ii. Member is not a candidate for either

II. Vismodegib (Erivedge) is considered investigational when used for all other conditions, including but not limited to:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome
   C. Prostate Cancer
D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Vismodegib (Erivedge) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**

IV. Member has a diagnosis of **metastatic or locally advanced basal cell carcinoma**; **AND**

V. Member has experienced a clinical response to therapy defined by improvement or stabilization of disease or decrease or stabilization of tumor size or spread; **AND**

VI. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with vismodegib (Erivedge).

Supporting Evidence

I. The safety and efficacy of vismodegib (Erivedge) in basal-cell carcinoma was evaluated in the pivotal ERIVANCE trial; a multicenter, international, two-cohort, open-label, single-arm study of 104 patients with metastatic basal-cell carcinoma (BCC) and those with locally advanced BCC who had inoperable disease or who were not a candidate for surgery. Patients with locally advanced disease were required to have had prior radiation therapy, unless contraindicated or inappropriate.

II. The primary efficacy endpoint was the independently assessed objective response rate (ORR) based on RECIST guidelines for metastatic disease or a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration for locally advanced disease. The key secondary endpoint was duration of response (DOR). The study met its primary endpoint in both cohorts with an ORR of 30% (95% confidence interval [CI], 16 to 48; P=0.001) in the group with metastatic BCC and 43% (95% CI, 30 to 56; P<0.001) in the group with locally advanced BCC. The median duration of objective response was 7.6 months for metastatic BCC (range, 2.1 to 11.1) and locally advanced BCC (range, 1.0 to 12.9).

III. During the ERIVANCE trial, all patients experienced at least one adverse event (AE), with the majority classified as grade 1 or 2 in severity, and 25% experienced at least one serious adverse
event. Of those who experienced a serious adverse event, seven patients experienced a fatal adverse event and 12% had an adverse event that led to discontinuation. Common adverse events included muscle spasms, dysgeusia, alopecia, fatigue and weight loss.

IV. Patients enrolled in the study were age 18 and older and concurrent antitumor (oncologic) therapy was not permitted. The safety and/or efficacy of use in pediatric and adolescent patients or in combination with other oncologic therapies has not been evaluated.

V. Vismodegib (Erivedge) carries a black box warning for Embryo-fetal toxicity, as this agent is known to cause embryo-fetal death or severe birth defects when administered to a pregnant woman. FDA-label advises women of reproductive potential and men to use effective contraception during therapy with vismodegib (Erivedge) and for 24 months after the final dose.

VI. Long-term safety and efficacy of vismodegib (Erivedge) was evaluated in a follow-up study of the ERIVANCE trial for 39 months after the final data cutoff date of the primary analysis. The primary end point was ORR, with key secondary endpoints including DOR and overall survival (OS). Of the 104 patients enrolled at baseline, 96 discontinued for the following reasons: disease progression (27.9%), patient decision to withdraw (26.0%), and AEs (21.9%). The ORR for the mBCC cohort was 48.5% [95% CI, 30.8-66.2] and 60.3% in the laBCC cohort [47.2-71.7]. Median DOR was 14.8 months for the mBCC cohort [7.4-16.6] with a median OS of 33.4 months; Median DOR was 26.2 months [9.0-37.6] and OS was not estimable.

VII. No new safety concerns arose during the follow-up study. Again, all patients enrolled in the study experienced one or more treatment emergent adverse events (TEAEs). The incidence of TEAEs increased between the time of the primary analysis and the final data cutoff date for the follow-up study and correlated with patients who had 12 or more months of exposure to vismodegib (Erivedge). Patients who received treatment for 12 months or more had higher rates of muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, and nausea. Deaths occurring during the study were considered by the investigator to be related to vismodegib (Erivedge).

VIII. Vismodegib (Erivedge) is currently recommended by NCCN guidelines for use in recurrent or advanced disease, with the caveat to be used in the FDA-approved indication of metastatic or locally advanced disease, with a category 2A recommendation.

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

Investigational or Not Medically Necessary Uses

I. Vismodegib (Erivedge) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome
C. Prostate Cancer
D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

* 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. Vismodegib (Erivedge) [Prescribing Information]. Genentech USA, INC. South San Francisco, CA. January 2012.

Policy Implementation/Update:

<table>
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voclosporin (Lupkynis™)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP232

Split Fill Management*

**Description**
Voclosporin (Lupkynis) is an orally administered calcineurin-inhibitor.

**Length of Authorization**
- Initial: Six months
- Renewal: 12 months

**Quantity Limits**

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<th>Quantity Limit</th>
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<tr>
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<td>7.9 mg capsules</td>
<td>Lupus Nephritis</td>
<td>180 capsules/30 days</td>
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**Initial Evaluation**

I. **Voclosporin (Lupkynis)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a rheumatologist or nephrologist; **AND**
   C. **Not** used in combination with biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of **Lupus Nephritis (LN)**; **AND**
      1. Biopsy indicating class III (focal), IV (diffuse), or V (membranous) LN; **AND**
      2. Biopsy shows active lesions; **OR**
         i. Biopsy shows active AND chronic lesions; **AND**
      3. Provider attestation indicating medication will be given in combination with mycophenolate (CellCept) for induction and maintenance; **AND**
      4. Provider attestation the member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated; **AND**
      5. Treatment with belimumab (Benlysta) has been ineffective, contraindicated, or not tolerated.
II. Voclosporin (Lupkynis) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Systemic Lupus Erythematosus (SLE) with absence of lupus nephritis
   B. Severe active central nervous system lupus
   C. Renal transplantation

**Renewal Evaluation**

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

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

III. A diagnosis of **Lupus Nephritis (LN)**; **AND**

IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria, improved/stable serum creatinine, reduction in urinary sediment); **AND**

V. Not used in combination with other biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**

VI. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated.

**Supporting Evidence**

I. LN is a kidney disease that develops in about 40% of patients with SLE. Approximately 10% of patients develop end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours [or spot urine protein-to-creatinine ratio (UPCR) >500 mg/g], unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.
   - Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
   - Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
   - Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
   - Class VI (advanced sclerosing): patients with sclerosing lesions; generally, do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.

II. European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) 2019 and 2012 American College of Rheumatology guidelines on LN recommend immunosuppressive therapy for LN starting with an induction phase to achieve a renal response.
which is recommended for the first six months of treatment, followed by maintenance therapy. Initial (induction) treatment is recommended with mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide, both combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone). Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no, or low-dose (< 7.5 mg/day), glucocorticoids. If a patient fails to respond to the first six months of induction therapy, guidelines suggest switching the immunosuppressive agent in combination with glucocorticoid pulse. Alternatively, calcineurin inhibitors (tacrolimus or cyclosporine) can be used as monotherapy or in combination with MMF as induction/maintenance therapy particularly in refractory cases.

III. Guidelines recommend patients with LN be treated with hydroxychloroquine or an equivalent antimalarial, unless contraindicated, and adjunctive therapies be added to manage LN and attenuate complications of the disease.

IV. The safety and efficacy of voclosporin (Lupkynis) in pediatric patients has not been established.

V. The safety and efficacy of voclosporin (Lupkynis) in combination with biologic therapies [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)] has not been evaluated.

VI. Per the package insert, use of voclosporin (Lupkynis) is not recommend in patients with a baseline eGFR less than or equal to 45 mL/min/1.73m² unless the benefit exceeds the risk, as these patients may be at increased risk for acute and/or chronic nefrotoxicity.

VII. Policy is specific to list MMF as the induction/maintenance therapy due to potential safety concerns of additive toxic effects that may occur when co-administering voclosporin (Lupkynis) and cyclophosphamide. Per the package insert, use of voclosporin (Lupkynis) in combination with cyclophosphamide has not been established and is not recommended. The FDA review of voclosporin (Lupkynis) further adds “given the adverse reaction profile of cyclophosphamide and the lack of efficacy data for voclosporin in combination with cyclophosphamide, the review team concluded that there is reasonable concern about the benefit-risk profile in this situation, thus necessitating this limitation of use”.

VIII. Voclosporin (Lupkynis) was evaluated as an adjunct to standard therapy in a Phase 3, randomized, double-blind, placebo-controlled, 52-week trial in adults (n=357) with biopsy proven LN. The primary efficacy outcome was complete renal response at week 52, defined as a UPCR < 0.5, eGFR ≥ 60 ml/min per 1.73 m² or a decline in no more than 20% from baseline, no rescue therapy, and a sustained dose ≤than 10 mg of prednisone. The primary endpoint was met with 73 patients (40.8%) in the voclosporin (Lupkynis) arm achieving renal response compared to 40 patients (22.5%) in the placebo arm (odds ratio 2.7; 95% CI: 1.6-4.3; P<0.001).

- All patients included in the trial were on background therapy with mycophenolate mofetil plus corticosteroids. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine (UPCR) of 2 or more (average patient had a baseline UPCR of 4), biopsy proven LN class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with, or without, coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within last 6 months. All patients also had biopsy specimens showing active lesions or active and chronic lesions.

IX. As of date there are no head to head trials comparing voclosporin (Lupkynis) to belimumab (Benlysta). Additionally, guidelines do not have recommendations around preferring either agent in the setting of LN. However, given the potential for chronic calcineurin inhibitor-related nephrotoxicity, especially relevant to this patient population with underlying renal disease, and
the insufficient long-term controlled safety data beyond one year, the plan requires trial of or contraindication to belimumab (Benlysta) prior to use of voclosporin (Lupkynis).

**Investigational or Not Medically Necessary Uses**

I. Voclosporin (Lupkynis) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Systemic Lupus Erythematosus (SLE) in absence of lupus nephritis (LN)
   B. Severe active central nervous system lupus
   C. Renal Transplantation

* 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**

7. FDA Center for Drug Evaluation and Research. Application number: 213716Orig1s000. Multi-Discipline review. Available at: [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000MultidisciplineR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000MultidisciplineR.pdf)

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<td>05/2021</td>
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Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP025

Description
Vonvendi is a recombinant von Willebrand factor indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease for on-demand treatment and control of bleeding episodes, and perioperative management.

Length of Authorization
- Initial: 6 months (for on-demand); 1 month (for perioperative)
- Renewal: 6 months (for on-demand)

Quantity limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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| Vonvendi, von Willebrand factor (recombinant) | 650, 1300 IU | On-demand treatment and control of bleeding episodes:  
- Minor: Up to 50 IU/kg for the initial dose, subsequent doses of up to 50 IU/kg every eight to 24 hours as clinically required  
- Major: Up to 80 IU/kg for the initial dose, subsequent doses of up to 60 IU/kg every eight to 24 hours for approximately two to three days, as clinically required  
Periodic management of bleeding: A dose may be given 12 to 24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery) | On-demand treatment and control of bleeding episodes: Up to the number of doses requested every 28 days  
Periodic management of bleeding: Up to the number of doses requested every 28 days |

Initial Evaluation
I. Vonvendi may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; AND
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; AND
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding when one of the following is met:  
         i. Member has severe vWD; OR
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.

ii. Member has mild or moderate vWD and the use of desmopressin is known or suspected to be ineffective or contraindicated; OR

2. Perioperative management of bleeding

II. Vonvendi is considered investigational when used for any other condition.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seek medical attention due to bleeding symptoms due to the mild nature of the disease in many patients, and to the lack of bleeding challenges.

II. There are three types of inherited vWD:

   - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
   - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size ratios or biologic properties).
   - Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.

III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).

IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF.

V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding. However, vWF is not generally given as long-term prophylaxis like is done in patients with hemophilia A.

VI. The safety and efficacy of Vonvendi was established based on a series of 22 patients with vWD over the age of 18 years of age who experienced 192 bleeding episodes (mostly mucosal, seven major). Results showed the Vonvendi was highly effective in restoring hemostasis. Most episodes were treated with a single infusion.
**Investigational or Not Medically Necessary Uses**

There is no evidence to support the use of Vonvendi in any other condition.

**References**


**Policy Implementation/Update:**

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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.

September 01, 2022
vorinostat (Zolinza®)
UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP217

Split Fill Management*

Description
Vorinostat (Zolinza) is an orally administered inhibitor of histone deacetylase (HDAC) enzymes (HDAC1, HDAC2, HDAC3 and HDAC6).

Length of Authorization
• Initial: Three months
• Renewal: 12 months

Quantity Limits

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<td>Vorinostat (Zolinza)</td>
<td>100 mg capsules</td>
<td>Cutaneous T-Cell Lymphoma</td>
<td>120 capsules/30 days</td>
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Initial Evaluation

I. Vorinostat (Zolinza) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; AND
   C. Medication will not be used in combination with any other oncolytic agent; AND
   D. Medication will not be used in combination with skin-directed therapies (e.g. Total Skin Electron Beam Therapy [TSEBT], phototherapy); AND
   E. Member has not progressed on, or after, prior treatment with HDAC inhibitor (e.g. romidepsin [Istodax]); AND
   F. A diagnosis of cutaneous T-cell lymphoma (CTCL) [i.e. Sezary syndrome, mycosis fungoides] when the following are met:
      1. Member has progressive (stage II or higher) or recurrent disease; AND
      2. Treatment with two or more of the following systemic regimens have been ineffective or not tolerated:
         i. Systemic retinoid (e.g. bexarotene [Targretin])
         ii. Methotrexate (oral or injectable)
         iii. Systemic chemotherapy (e.g. chlorambucil, cyclophosphamide, etoposide)
         iv. Targeted immunotherapy (e.g. mogamulizumab, brentuximab)
         v. Interferons (e.g. peginterferon-alfa 2b [PegIntron], interferon gamma [Actimmune])

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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.

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

- Malignant pleural mesothelioma
- Cutaneous B-cell lymphoma
- Multiple myeloma
- Hodgkin’s lymphoma

Renewal Evaluation

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

II. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**

III. Member has experienced response to treatment (e.g. complete or partial remission, decrease from baseline in SWAT skin assessment scores, or PGA scores)

Supporting Evidence

I. Vorinostat (Zolinza) is FDA-approved for the treatment of cutaneous manifestations in adult patients with cutaneous T-cell lymphoma (CTCL), who have progressive, persistent, or recurrent disease on, or following, 2 systemic therapies. Its approval was based on results from 2 single-arm, open-label trials. Efficacy and safety of vorinostat has not been studied in pediatric population.

II. Sézary syndrome (SS) and mycosis fungoides (MF) are the most common subtypes of advanced cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin, but lymph nodes, blood, and viscera may also be involved. Skin lesions include erythroderma, patches, plaques, or tumors that may be localized or widespread. SS is a distinctive erythrodermic CTCL with leukemic involvement of malignant T cells that typically match the clone in the skin; less frequently, distinct clones may be detected in skin and blood.

III. Advanced stage MF and SS are most often chronic with a persistent or relapsing course. The choice of therapy at different time points in the disease is largely dependent on the goals of therapy, which include long-term disease control and prompt symptom relief. Therefore, management of advanced and recurrent CTCL is often orchestrated by a multidisciplinary team comprised of dermatologists, medical oncologists, and radiation oncologists.

IV. Patients with early stage CTCL are treated with skin-directed therapies. A randomized trial demonstrated that early aggressive therapy with combination chemotherapy plus total skin electron beam radiation therapy (TSEBT) does not appear to improve survival when compared with the use of sequential topical regimens. Skin directed therapies include topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), retinoids, imiquimod, and phototherapy (UVB or PUVA). There is no standard initial therapy, and experts differ in their preferred approach. Alternatively, for patients with generalized tumors (e.g., >10 percent body surface area), equally acceptable treatment options are the use of total skin electron beam therapy (TSEBT) and systemic therapies. TSEBT often provides a complete response (CR), albeit temporary in most cases, while systemic agents generally provide partial responses but can be given in a maintenance fashion. A choice among these treatments is made based on patient preference and clinician experience. Despite decades of experience in the treatment of SS and
MF, well-designed, prospective, controlled clinical studies comparing the efficacy of various therapies are lacking.

V. NCCN guideline for the treatment of recurrent or advanced CTCL (MF and SS) includes vorinostat (Zolinza) as one of the preferred regimens (category 2A recommendation). Systemic therapies in this space generally involve use of single agents. Multiagent chemotherapy regimens are reserved for patients, who have progressed after multiple agents in the preferred regimens (e.g. bexarotene, brentuximab, interferons, methotrexate, mogamulizumab, romidepsin). Participants in the clinical trials for vorinostat (Zolinza) did not have a history of prior treatment with an HDAC inhibitor. Efficacy and safety of vorinostat (Zolinza) after progression on another HDAC inhibitor (e.g. romidepsin) has not been studied. Additionally, Safety of combining TSEBT and phototherapy with vorinostat (Zolinza) is unknown. NCCN guideline for primary T-Cell lymphoma recommend against such combination regimen.

VI. In an open-label, single-arm, multicenter, nonrandomized clinical trial (N= 74), patients (median age 61 years) with advanced refractory CTCL were treated with vorinostat (400 mg daily). An objective clinical response of 30% was reported with median duration of response 4 weeks. The majority of patients (82.4%) had stage IIB and higher CTCL and had previously failed a median of 3 prior systemic therapies (range, 1 to 12). The primary efficacy endpoint was measured as either a complete clinical response or partial response (i.e. ≥ 50% decrease in a modified severity weighted assessment tool (SWAT) score from baseline) ORR was 29.7% (n= 22) (95% CI; 19.7, 41.5) The median times to response for the overall population and individuals with stage IIB and higher CTCL was 55 days and 56 days (range, 28 to 171 days), respectively. The median time to tumor progression (50% increase in the SWAT score from the nadir) was 202 days. Response to previous systemic therapy was not a response predictor to vorinostat.

VII. In a phase 2, open-label, single-center, nonrandomized trial (n=33, median age 67 years), vorinostat exhibited treatment response among previously-treated patients with relapsed or refractory CTCL. The majority (85%) patients had stage IIB and higher CTCL, and were refractory to, or intolerant to, prior systemic therapies (median, 5; range, 1 to 15). Patients were assigned to one of the 3 groups: group 1: vorinostat 400 mg daily (n=13); group 2: vorinostat 300 mg twice daily for 3 days with 4 days rest (n=11) and group 3: vorinostat 300 mg twice daily for 14 days with 7 days rest, followed by 200 mg twice daily (n=9). Oral retinoids, vitamin A or alternative medicines were not allowed. Physician’s global assessment (PGA) scores were used for assessing improvement/ partial response. Based on the intent-to-treat analysis, the ORR were 31%, 9%, and 33% in groups 1, 2, and 3, respectively. The ORR was 24.2% (n= 8) in the overall population, 25% (n= 7) in individuals with stage IIB or higher disease, and 36.4% (n= 4) in patients with Sezary syndrome.

VIII. During clinical trials, participants receiving vorinostat (Zolinza) reported significant adverse reactions and drug toxicity events. Fatigue (73%), thrombocytopenia (54%), diarrhea (49%), nausea (49%), and dysgeusia (46%) were the most common adverse drug reactions leading to dose reductions. Overall, 19% participants discontinued treatment due to adverse reactions. Vorinostat has been included in the Institute for Safe Medication Practices (ISMP) list of drug classes, which have a heightened risk of causing significant patient harm when used in error.
Investigational or Not Medically Necessary Uses

I. There is insufficient evidence to support the use of vorinostat (Zolinza) for conditions other than cutaneous T-cell lymphoma.

   A. Malignant pleural mesothelioma: Vorinostat (Zolinza) showed some evidence of efficacy in an initial phase I study. However, extensive evaluation did not confirm a clinically meaningful benefit from this approach. In a phase III trial, 661 previously treated patients were randomly assigned to either vorinostat or placebo. Progression free survival (PFS) was prolonged with vorinostat (median, 6.3 weeks versus 6.1 weeks; hazard ratio [HR] 0.75, 95% CI 0.63-0.88). However, this increase was not clinically significant. Also, the difference in overall survival was not significant (median, 30.7 weeks versus 27.1 weeks; HR 0.98, 95% CI 0.83-1.17).

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

References


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<td>01/2021</td>
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<td>Criteria reviews and updates</td>
<td>09/2012; 12/2012; 01/2013</td>
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<td>03/2012</td>
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Description
Vosoritide (Voxzogo) is a daily subcutaneously administered C type natriuretic peptide.

Length of Authorization
- Initial: Six months
- Renewal: Six months

Quantity Limits

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Initial Evaluation

I. **Vosoritide (Voxzogo)** may be considered medically necessary when the following criteria are met:
   A. Member is 5 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a pediatric specialist in one of the following areas: neurology, orthopedic surgery, endocrinology, genetics; **AND**
   C. A diagnosis of achondroplasia; **AND**

   1. Provider attestation to the following:
      i. Genetic testing has been done to confirm diagnosis; **AND**
      ii. Epiphyses are open, as confirmed by radiographic imaging completed in the previous three months; **AND**
      iii. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
      iv. Limb lengthening surgery has not been performed in the past 18 months; **AND**
      v. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**

   2. Documentation of the following, measured within the past three months (necessary for dose calculation and renewal information):
      i. Annualized growth velocity (AGV); **AND**
      ii. Member weight
II. Vosoritide (Voxzogo) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Forms of dwarfism other than achondroplasia
   B. For growth in patients with achondroplasia when epiphyses are closed
   C. Achondroplasia in patients under five years of age
   D. Combination therapy with growth hormone treatment or limb-lengthening surgery

**Renewal Evaluation**

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

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

III. Provider attestation to the following:
   A. If the member is 12 years of age or older or if epiphyses could be closed (e.g., precocious puberty, no height gained in previous few months): radiographic imaging on long bones has been completed within the past year to confirm epiphyses remain open (i.e., potential for growth still remains); **AND**
   B. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
   C. Limb lengthening surgery has not been performed in the past 18 months; **AND**
   D. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**

IV. Documentation of the following, measured within the past three months:
   A. Annualized growth velocity (AGV); **AND**
   B. Member weight; **AND**

V. Documentation that the most recent annualized growth velocity (AGV) is greater than the baseline AGV

**Supporting Evidence**

I. Vosoritide (Voxzogo), is FDA-approved to increase linear growth in pediatric patients with achondroplasia. It is a daily subcutaneous (SC) injection with dose based on patient body weight. It has not been evaluated for safety and efficacy, and is not FDA-approved in patients under five years of age. Clinical trial enrollment should be considered for patients under five years of age until further safety and efficacy in this population has been sufficiently evaluated.

II. Achondroplasia is a condition of disproportionate short stature and affects 1:20,000 births. Gene mutations permanently activate the FGFR3 receptors, inhibit chondrocyte proliferation, and impair bone formation. Vosoritide (Voxzogo) is the first pharmacotherapy FDA-approved for this condition. There are no formal U.S. guidelines for the treatment of achondroplasia; however, management is highly specialized. Thus, a specialist prescriber is required.

III. Achondroplasia is caused by variants in the FGFR3 gene, and is recognized on genetic testing. Vosoritide (Voxzogo) targets the root cause of the condition, and safety and efficacy in other
causes of forms of dwarfism are unknown, and is not expected to increase linear growth in other conditions. To rule out other causes or forms of dwarfism, genetic testing is required.

IV. Outside of lifestyle management (e.g., adaptation of home and school environments) and adjunctive care (e.g., treatment for sleep apnea), limb lengthening surgery may be considered. Surgery may be performed at any time, prior to or after epiphses (i.e., growth plate) close. Evidence suggests there is greater success with surgery after epiphyses have closed. Therapy has not been evaluated for safety and efficacy in those that have received limb lengthening surgery within the past 18 months, or in conjunction with limb lengthening surgery. If surgery has been completed, vosoritide (Voxzogo) therapy should not be used within an 18-month window of surgery, to realize the benefits of surgical intervention. Furthermore, safety and efficacy of this therapy in conjunction with or to prepare for surgery has not been evaluated. Additionally, it is unknown if use of vosoritide (Voxzogo) will have additive effects if used prior to surgery; thus, if surgery is planned or expected prior to final height being reached (e.g., closed epiphyses), therapy should be discontinued.

V. Vosoritide (Voxzogo) is not expected to provide further linear growth after epiphyses close. FDA and manufacturer guidance indicate that if epiphyses close, therapy should be discontinued at this time. Additionally, therapy should not be initiated in patients that have epiphysial closure. Routine imaging should be completed to evaluate medical necessity for therapy, and is required for initiation of therapy, as well as for renewal evaluation in patients of 12 years of age and older given the greater potential of epiphysial closure at adolescence.

VI. Growth hormone therapy is controversial in patients with achondroplasia. It is not commonly used in the U.S. as evidence suggests this may exacerbate the disproportionate stature; however, evidence is conflicting. Dual therapy has not been evaluated for safety or efficacy; thus, concurrent use is not allowed.

VII. Vosoritide (Voxzogo) was evaluated in a Phase 3, randomized, blinded, placebo-controlled trial in 121 patients that were at least five years of age. Baseline AGV was around 4 cm/year for all patients. The primary outcome was an increase in annualized growth velocity (AGV) over baseline, which was statistically significant for vosoritide (Voxzogo) over placebo with an increase in AGV of 1.71 cm/year, compared to 0.13 cm/year. Therapy was also evaluated in a one-year, open-label extension trial where patients could continue therapy, and those originally randomized to placebo were switched to vosoritide (Voxzogo). The crossover group achieved an AGV of 1.62 cm/year, further supporting the pivotal trial results that therapy may influence an increase a 1.5-1.6 cm increase in AGV. Vosoritide (Voxzogo) has not yet shown to improve other disease manifestations, function, QoL, or reduction surgical intervention need. Vosoritide (Voxzogo) was granted Priority Review, Accelerated Approval, and Orphan Drug Designations. There will be a long-term, open-label trial to evaluate the drug’s impact on final height. To assess if there has been an increase in AGV for patients on vosoritide (Voxzogo) therapy, a recently measured baseline AGV is required prior to initiation, as well as upon each renewal to determine if there is a continued treatment effect. In absence of continued treatment effect, continuation of therapy is not warranted at this time.

VIII. Vosoritide (Voxzogo) is weight based; thus, a recent weight from growing pediatric patients is required for initial and renewal coverage considerations for appropriate dose calculation.
Investigational or Not Medically Necessary Uses

I. Vosoritide (Voxzogo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Forms of dwarfism other than achondroplasia. Vosoritide (Voxzogo) counteracts the genetic mutation that causes achondroplasia. In addition to lack of evidence for safety and efficacy, there is no expectation that therapy would be effective for other conditions, including other forms of dwarfism or short stature (e.g., growth hormone deficiency, Turner syndrome).
   B. For growth in patients with achondroplasia when epiphyses are closed
   C. Achondroplasia in patients under five years of age
   D. Combination therapy with growth hormone treatment or limb-lengthening surgery

References


Policy Implementation/Update:

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<td>Policy created</td>
<td>02/2022</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description
Voxelotor (Oxbryta) is an orally administered hemoglobin S (HbS) polymerization inhibitor.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<td>300 mg soluble tablet</td>
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<td></td>
<td>10 - &lt;20 kg</td>
<td>60 tablets/30 days</td>
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<td></td>
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<td>&gt;40 kg</td>
<td>150 tablets/30 days</td>
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Initial Evaluation

I. **Voxelotor (Oxbryta)** may be considered medically necessary when the following criteria are met:
   A. Member is 4 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 crizanlizumab-tmca (Adakveo); **AND**
   D. A diagnosis of **sickle cell disease (SCD)** when the following are met:
      1. Baseline hemoglobin level is ≤ 10.5 g/dL; **AND**
      2. Treatment with both the following have been ineffective, contraindicated, or both are not tolerated:
         i. Hydroxyurea (generic, Siklos, Droxia) for a minimum duration of six months; **AND**
         ii. L-glutamine (available over-the-counter); **AND**
      3. If requesting **soluble** tablets, member must demonstrate a medical reason they are unable to utilize oral tablets (e.g., weight, difficulty swallowing, oral/motor difficulties, feeding tube administration). Convenience of administration route does not equate to medical necessity

II. Voxelotor (Oxbryta) is considered **investigational** when used for all other conditions, **AND** when used in combination with crizanlizumab-tmca (Adakveo).
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 established 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. Use of voxelotor (Oxbryta) is not in combination with crizanlizumab-tmca (Adakveo); AND

IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced vaso-occlusive crises (VOCs) compared to baseline, increase in hemoglobin levels, maintained increased hemoglobin levels); AND

V. If requesting soluble tablets, the member must demonstrate a medical reason they are unable to utilize oral tablets (e.g., weight, difficulty swallowing, oral/motor difficulties, feeding tube administration)

Supporting Evidence

I. Approval for voxelotor (Oxbryta) occurred following the phase 3 pivotal HOPE trial (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization). Subjects were between 12 to 65 years of age with confirmed sickle cell disease with documentation of one to 10 vaso-occlusive events within the past 12 months and baseline hemoglobin levels between 5.5 and 10.5 g/dL. Efficacy was based on hemoglobin response rate defined as a hemoglobin increase of >1 g/dL from baseline. The trial reported a response rate of 51.1% (46/90) compared to 6.5% (6/92) in the placebo group (p < 0.001).

II. The efficacy in younger pediatric patients was evaluated in the single arm, open label, HOPE-KIDS 1 trial which included patients aged 4 to <12 years old. Patients in the HOPE-KIDS 1 trial had a baseline hemoglobin ≤10.5 g/dL and 80% were on background hydroxyurea therapy. Previous vaso-occlusive event was not required. Similar to the HOPE trial, the primary outcome in HOPE-KIDS 1 was hemoglobin response rate, which was reported as 36% (16/45) (95% CI: 21.6%, 49.5%).

III. Voxelotor (Oxbryta) was approved under accelerated approval based on increase in hemoglobin. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial. There are no data to support an increase in hemoglobin level results in a reduction in vaso-occlusive events, or other complications related to sickle cell disease. Hemoglobin represents one of many factors contributing to vaso-occlusive events. Voxelotor (Oxbryta) approval was based on increase in hemoglobin and all patients included in trials had hemoglobin levels ≤10.5 g/dL, clinical necessity of voxelotor (Oxbryta) in patients with hemoglobin levels >10.5 g/dL is unknown. Per the American Society of Hematology (ASH), for patients with sickle cell disease receiving simple transfusions, the point of diminishing benefit of arterial oxygen delivery is estimated to be between 10 and 11 g/dL; beyond this point any increase in hemoglobin concentration decreases the arterial oxygen delivery.

IV. Acute complications and symptoms occur intermittently in sickle cell disease and throughout its course. These complications include vaso-occlusive pain crises (VOCs), acute chest syndrome, aplastic crisis, hemolytic crisis, and the pooling of blood within bodily organs. Vaso-occlusive
carnes (VOCs) include stroke, severe pain, kidney and other organ and/or tissue damage for which there is no other explanation than vaso-occlusive crisis. Transfusion protocol is considered the most effective therapy for secondary stroke prophylaxis. If this is contraindicated or ineffective, hydroxyurea is introduced.

**V. Hydroxyurea:** Generic hydroxyurea is considered first-line in the treatment of sickle cell disease. Typically offered to patients with three or greater sickle cell-associated moderate-to-severe crises within the last 12 months. Has been shown to be disease modifying at reducing the rate of pain episodes, stroke, transfusion requirement, and mortality. Has been shown to reduce the number of VOCs and hospitalizations. The majority of subjects in the HOPE and HOPE-KIDS 1 trials were established on hydroxyurea at baseline.

**VI. L-glutamine:** Typically considered in patients who have at least two VOCs per year, despite maximally tolerated hydroxyurea dose, and considered against cost. Was approved to reduce acute complications of sickle cell disease (VOCs). Monotherapy is considered in patients who do not tolerate hydroxyurea. Over-the-counter products are available as well as in a prescription product L-glutamine (Endari)

**VII.** Both hydroxyurea and L-glutamine have evidence to support disease-modifying activity and the reduction of VOC or complications related to disease.

**VIII.** In children 12 years and older, as well as in adults, voxelotor (Oxbryta) is dosed as 1,500 mg daily. Children ages 4 to less than 12 years old follow weight-based dosing as noted in the table below.

<table>
<thead>
<tr>
<th>Weight</th>
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<tr>
<td>10 – 19 kg</td>
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<td>20 – 39 kg</td>
<td>900 mg once daily</td>
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<td>&gt;40 kg*</td>
<td>1,500 mg once daily</td>
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*Medical necessity for 300 mg soluble tablets is required for members weighing 40 kg or greater; as the recommended dose (1,500 mg daily) can be obtained with the 500 mg oral tablet, providing a significant price differential (~2.5x difference).

**Investigational or Not Medically Necessary Uses**

**I.** There is currently limited to no data to support the safety and efficacy of concomitant use of voxelotor (Oxbryta) with crizanlizumab-tmca (Adakveo).

* 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.

Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
References


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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description
Zanubrutinib (Brukinsa) is an orally administered Bruton’s Tyrosine Kinase (BTK) inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

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<td>Treatment of Waldenström’s macroglobulinemia in adults</td>
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<td></td>
<td>Treatment chronic lymphocytic leukemia or small lymphocytic lymphoma in adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen</td>
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Initial Evaluation

I. Zanubrutinib (Brukinsa) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist, or hematologist; AND
   C. Medication will not be used in combination with any other oncolytic medication; AND
   D. Member has not previously progressed on a BTK inhibitor [e.g., ibrutinib (Imbruvica), acalabrutinib (Calquence)]; AND
   E. A diagnosis of one of the following:
      1. Waldenström’s Macroglobulinemia (WM); AND
         i. Member has received one prior therapy [e.g., chemotherapy, rituximab (Rituxan)]; OR
         ii. Provider attestation that member is not a candidate for standard immunochemotherapy based on documented risk factors or comorbidities

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.
2. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; AND
   i. Medication is used in the relapsed/refractory setting; **AND**
   ii. Member has received one prior therapy [e.g., chemotherapy, venetoclax (Venclexta), obinutuzumab (Gazyva)]; **AND**
   iii. Member has a documented intolerance or contraindication to other BTK inhibitors [e.g., ibrutinib (Imbruvica), acalabrutinib (Calquence)]

II. Zanubrutinib (Brukinsa) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Diffuse Large B-cell Lymphoma (DLBCL)
   B. Follicular Lymphoma (FL)
   C. Hairy Cell Leukemia (HCL)
   D. Graft-versus Host Disease (GvHD)
   E. Marginal Zone Lymphoma (MZL)
   F. Indolent Non-Hodgkin Lymphoma (iNHL)
   G. MCL monotherapy
   H. MCL first-line therapy
   I. MCL combination therapy
   J. Richter's Transformation

Renewal Evaluation

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

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms (e.g. no signs of disease progression); **AND**

IV. Zanubrutinib (Brukinsa) will not be used in combination with any other oncolytic medication

Supporting Evidence

I. **WM:**
   A. Zanubrutinib (Brukinsa) is FDA-approved for WM based on the non-comparative assessment of DOR from zanubrutinib (Brukinsa) treatment arms and was granted Fast Track and Orphan Drug designation.
   B. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 77 WM patients and one head-to-head trial against ibrutinib (ASPEN). ASPEN was a Phase 3, randomized, active control, open-label trial which enrolled 137 relapsed/refractory (RR) and 37 treatment naïve WM adult patients. Median number of previously tried therapies included 1 (range: 1-8) and majority (90%) were refractory to anti-CD20 therapies (rituximab, ofatumumab), alkylating agents (88%) (cyclophosphamide, chlorambucil, bendamustine), and glucocorticoids (72%).
Treatment naïve patients consisted of those unsuitable for standard immunochemotherapy based on presence of comorbidities or risk factors precluding its use (e.g., age, cardiac, renal, infection comorbidities). Median patient age was 70 years of age. The trial excluded patients with previous exposure to BTK inhibitor therapy and those with WM central nervous system involvement. The primary endpoint of proportion of patients achieving very good partial response (VGPR) or CR was not reached. The trial efficacy analysis used hierarchical sequence; thus, all secondary endpoints were considered exploratory. Secondary endpoint of median PFS was not estimable, but 18-month PFS was 85% for zanubrutinib (Brukinsa) and 84% for ibrutinib. Median OS was not estimable at the time of analysis, but 18-month OS was 97% for zanubrutinib (Brukinsa) and 93% for ibrutinib.

C. Zanubrutinib (Brukinsa) had lower rates of atrial fibrillation (2% vs 15%), hypertension (11% vs 16%), minor bleeding (48.5% vs 59.2%), major hemorrhage (5.9% vs 9.2%), and diarrhea (20.8% vs 31.6%) compared to ibrutinib, respectively. The rate of neutropenia was 29.7% and 13.3% for zanubrutinib (Brukinsa) and ibrutinib, respectively.

D. NCCN guidelines recommend the following preferred therapies for the treatment of primary, and previously treated, WM: bendamustine/rituximab, bortezomib/dexamethasone/rituximab, ibrutinib ± rituximab (category 1), rituximab/cyclophosphamide/dexamethasone, and zanubrutinib (Brukinsa) (category 1).

II. CLL/SLL:

A. Zanubrutinib (Brukinsa) is not FDA-approved for the treatment of CLL/SLL as of December 2021. Zanubrutinib (Brukinsa) was studied in one phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 101 patients with treatment relapsed/refractory CLL or SLL; one phase 2, open-label, single-arm trial (BGB-3111-205) in 91 Chinese patients with relapsed/refractory CLL or SLL; and one phase 3, randomized, open-label, head-to-head study against ibrutinib (ALPINE). The ALPINE study included 600 adult patients with relapsed/refractory CLL or SLL who have tried ≥1 prior systemic therapy consisting of ≥2 cycles of treatment. Majority of patients (62%) were ≥65 years of age without high risk mutations (81%). At the time of data cut-off, results were available for 415 enrolled patients with a median follow up of 15 months. Interim primary endpoint data shows statistically significant ORR in zanubrutinib (Brukinsa) arm compared to ibrutinib (78.3% vs 62.5%, p=0.006). ORR in participants with del11q and del17p mutations was also numerically higher for zanubrutinib (Brukinsa) arm. PFS was estimated at 12 months but was not a prespecified endpoint and was numerically higher for zanubrutinib (Brukinsa) than ibrutinib arm (94.9% vs 84.9%). Twelve-month OS data was numerically higher in zanubrutinib (Brukinsa) arm over ibrutinib (97% vs 92.7%). Interim results indicate promising efficacy for zanubrutinib (Brukinsa); however, complete efficacy results are needed to further assess any superiority claims. Safety profile was comparable between the two treatment arms except, zanubrutinib (Brukinsa) had a higher incidence of neutropenia compared to ibrutinib (28.4% vs 21.7%) and a lower incidence of atrial fibrillation/flutter (2.5% vs 10.1%) at the time of data cut-off.

B. Comparative efficacy between zanubrutinib (Brukinsa) and other BTK inhibitors (e.g., ibrutinib [Imbruvica], acalabrutinib [Calquence]) remains unknown at this time. Once available, finalized ALPINE trial results will further inform comparative efficacy and safety between zanubrutinib (Brukinsa) and ibrutinib (Imbruvica). There is more confidence in the...
efficacy and safety of ibrutinib (Imbruvica) and acalabrutinib (Calquence) than zanubrutinib (Brukinsa) at this time due to availability of multiple randomized clinical trials showing greater PFS when compared to active comparators used in relapsed/refractory CLL/SLL as well as longer time on the market. As of December 2021, NCCN guidelines reserve the use of zanubrutinib (Brukinsa) only in cases of previous intolerance or a contraindication to other BTK inhibitors.

C. NCCN guideline (Version 1.2022 – September 8, 2021) recommended therapies are divided by mutation status, age, and comorbidities. Preferred second-line and subsequent regimens for those without del(17p)/TP53 mutation are the same for patients of all ages, with, or without, comorbidities, and include acalabrutinib (category 1), ibrutinib (category 1), and venetoclax + rituximab (category 1). Zanubrutinib (Brukinsa) is included as other recommended regimens for patients with intolerance or contraindication to other BTK inhibitors along with bendamustine + rituximab (only <65 years old), duvelisib, FCR (only <65 years old), idelalisib ± rituximab, lenalidomide ± rituximab, obinutuzumab, ofatumumab, venetoclax, chlorambucil + rituximab (only ≥65 years old or <65 with comorbidities) (all category 2A) and certain category 2B and category 3 regimens. For patients with del(17p)/TP53 mutations, chemoimmunotherapy is not recommended since del(17p)/TP53 mutation is associated with low response rates. Preferred second-line and subsequent regimens include acalabrutinib (category 1), ibrutinib (category 1), venetoclax + rituximab (category 1), and venetoclax (category 2A). Zanubrutinib (Brukinsa) is included as other recommended regimens for patients with intolerance or contraindication to other BTK inhibitors along with alemtuzumab ± rituximab, duvelisib, HDMP + rituximab, idelalisib ± rituximab, lenalidomide ± rituximab, and ofatumumab (all category 2A).

Investigational or Not Medically Necessary Uses

I. The following indications do not have sufficient evidence to support the use of zanubrutinib (Brukinsa) at this time:
   A. Diffuse Large B-cell Lymphoma (DLBCL)
   B. Follicular Lymphoma (FL)
   C. Hairy Cell Leukemia (HCL)
   D. Graft-versus Host Disease (GvHD)
   E. Marginal Zone Lymphoma (MZL)
      1. For the treatment of MZL, zanubrutinib (Brukinsa) is FDA-approved under the accelerated approval pathway based on ORR and DOR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Finalized data have not been published on these trials at this time.
      2. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies including 20 previously treated MZL patients (BGB-3111-AU-003) and one Phase 2, open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least 1 prior anti-CD20-based regimen (MAGNOLIA). MAGNOLIA study included patients with a median age of 70 years (range: 37 to 85), 38% had extranodal MZL, 38% nodal,
18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 88% of patients having prior rituximab-based chemotherapy, 32% had refractory disease at study entry. ORR was reached in 45 (68.2%) patients while DOR was not reached at the time of data analysis. Twelve-month DOR, PFS, and OS was as 93.0%, 82.5%, and 95.3%, respectively.

3. The most common adverse events were similar to adverse events seen in clinical trials studying other cancer types and included diarrhea, contusion, constipation, pyrexia, and upper respiratory tract infections. Serious adverse events occurred in 38.2% of patients and included COVID-19 pneumonia, pyrexia, and fall. Four patients discontinued treatment due to adverse events and 29.4% of patients had dose interruption due to adverse events.

4. Treatment of MZL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trials (single-arm, open-label study designs) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MZL.

5. NCCN guidelines recommend anti-CD20 based regimens as preferred therapies in second-line and subsequent setting as well as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ibrutinib, lenalidomide + rituximab, and zanubrutinib with a Category 2A recommendation. Other recommend regimens additionally umbralisib and PI3K inhibitors in patients relapsed/refractory after 2 prior therapies.

F. Indolent Non-Hodgkin Lymphoma (iNHL)

G. MCL monotherapy

1. For the treatment of MCL, zanubrutinib (Brukinsa) was FDA-approved under the accelerated approval pathway based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials; however, finalized data has not been published on these trials at this time.

2. Zanubrutinib (Brukinsa) was studied in one open-label, single-arm, Phase 2 trial (BGB-3111-206), and one Phase 1/2 safety and pharmacokinetic trial (BGB-3111-AU-003) in 118 patients with MCL who had progressed on prior systemic therapy. The primary efficacy outcome was ORR which was 84% in both trials. Secondary efficacy outcomes were complete response (CR), partial response (PR), and duration of response (DOR). The percentage of patients with a CR was 59% and 22% for the Phase 2 trial and Phase 1/2 trial, respectively. The percentage of patients with a PR was 24% and 62% for the Phase 2 trial and Phase 1/2 trial, respectively. Median DOR in months was 19.5 and 18.5 for the Phase 2 trial and Phase 1/2 trial, respectively. Progression-free survival was evaluated in the Phase 2 trial and found 74.6% of patients at 12 months were progression-free.

3. Treatment of MCL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trial (single-arm, open-label study design) with unknown clinical
impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MCL.

H. MCL first-line therapy
I. MCL combination therapy
J. Richter’s Transformation

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

References


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</tbody>
</table>
Please see the UMP Preferred Drug list for more details on prescription drugs that have step requirements:

<table>
<thead>
<tr>
<th>PEBB</th>
<th><a href="https://ump.regence.com/pebb/benefits/prescriptions">https://ump.regence.com/pebb/benefits/prescriptions</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>SEBB</td>
<td><a href="https://ump.regence.com/sebb/benefits/prescriptions">https://ump.regence.com/sebb/benefits/prescriptions</a></td>
</tr>
</tbody>
</table>
We follow federal civil rights laws. We do not discriminate based on race, color, national origin, age, disability, gender identity, sex or sexual orientation.

We provide free services to people with disabilities so that they can communicate with us. These include sign language interpreters and other forms of communication.

If your first language is not English, we will give you free interpretation services and/or materials in other languages.

If you need any of the above, call Customer Service at:
1-888-361-1611 (TRS: 711)

If you think we did not offer these services or discriminated, you can file a written complaint. Please mail or fax it to:
Washington State Rx Services
Attention: Appeal Unit
PO Box 40168
Portland, OR 97240-0168
Fax: 1-866-923-0412

Dave Nesseler-Cass coordinates our nondiscrimination work:
Dave Nesseler-Cass,
Chief Compliance Officer
601 SW Second Ave.
Portland, OR 97204
855-232-9111
compliance@modahealth.com

You can also file a civil rights complaint with:
The U.S. Department of Health and Human Services,
Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue, SW Room 509F, HHH Building Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD).

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html


Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx
ATENCIÓN: Si habla español, hay disponibles servicios de ayuda con el idioma sin costo alguno para usted. Llame al 1-888-361-1611 (TRS: 711).


注意：如果您说中文，可得到免費語言幫助服務。請致電 1-888-361-1611（聾啞人專用 TRS: 711）。

주의: 한국어로 무료 언어 지원 서비스를 이용하시려면 다음 연락처로 연락해주시기 바랍니다. 전화 1-888-361-1611 (TRS: 711)。


تنبيه: إذا كنت تتحدث العربية، فهناك خدمات مساعدات لغوية متاحة لك مجانًا. اتصل برقم 1-888-361-1611 (TRS: 711).

保護者: 若您以泰國為母語，您亦可獲免費的語言支援服務。請致電 1-888-361-1611 (TRS: 711)。

УВАГА! Якщо ви говорите українською, для вас доступні безкоштовні консультації рідною мовою. Зателефонуйте 1-888-361-1611 (TRS: 711).

ATTENTION : si vous êtes locuteurs francophones, le service d’assistance linguistique gratuit est disponible. Appelez au 1-888-361-1611 (TRS: 711).