Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 12/14/2023

Rivfloza™ (nedosiran)

HCPCS: J3490

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by genetic testing of the AGXT mutation
   b. FDA approved age
   c. Patient has an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2
   d. Patient does not have a history of kidney or liver transplant
   e. Trial and failure to at least 3 months, contraindication, OR intolerance to a course of high-dose vitamin B-6 therapy
   f. The member will self-administer Rivfloza unless clinically unable to do so
   g. Will not be used in combination with Oxlumo
   h. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Rivfloza is a small interfering ribonucleic acid (siRNA) that inhibits the production of the hepatic lactase dehydrogenase (LDH) enzyme – an enzyme that is involved in the conversion of glyoxylate to oxalate. Rivfloza is approved to lower urinary oxalate levels in children 9 years of age and older and adults with PH1 and relatively preserved kidney function, e.g., eGFR ≥ 30 ml/min/1.73 m^2.

- Primary hyperoxaluria (PH) is an ultra-rare genetic disease characterized by recurrent kidney and bladder stones. There are three types of PH that differ in their severity and underlying genetic mutation: PH1, PH2, and PH3. PH1 is the most common form of PH, accounting for around 80% of total cases and affecting approximately 3,000 to 5,000 patients in the US. PH1 patients have a mutation of the AGXT gene, which results in decreased or absent hepatic enzyme alanine-glyoxylate aminotransferase (AGT). AGT converts glyoxylate to glycine, and a decrease or absence of AGT brings about an increase in glyoxylate and oxalate. The excess production of oxalate by the liver results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones, nephrocalcinosis, progression to kidney failure, and systemic organ dysfunction. PH1 can be suspected in patients with increased urinary oxalate excretion, indicated by levels >1 mmol/1.73 m^2 per day. Genetic testing for a mutation in the AGXT gene confirms the PH1 diagnosis.

- Conservative treatment is generally recommended following a diagnosis of PH1, which includes hyperhydration, alkalizing the urine, and trialing pyridoxine. Hyperhydration is a common supportive measure for management of PH1. Increasing fluid intake to 3 L/m^2 body surface area (BSA) per day can create higher urinary output, which decreases tubular fluid oxalate concentration and intratubular deposition, thereby preventing oxalate accumulation in the kidney. Experts recommend this approach of increasing fluid intake to help manage PH1. Pediatric patients may require a gastronomy tube to meet the high daily fluid requirement. Urinary alkalinization should also be started to prevent stone formation. Potassium citrate (0.1 to 0.15 g/kg) can be used to decrease the amount of calcium oxalate. The citrate component will allow calcium citrate to form, which is much more soluble than calcium oxalate. Urinary pH must be kept between 6.2 and 6.8 to be alkaline.

- Prior to the approval of Oxlumo, high-dose vitamin B-6 (pyridoxine), a cofactor for the AGT enzyme, was the only treatment proven to target the underlying pathophysiology of PH1. In 30-50% of PH1 patients, vitamin B-6 reduces oxalate levels and prevents accumulation in the kidneys. Responsiveness to vitamin B-6 is defined as a >30% decrease in urinary oxalate excretion after a minimum trial period of 3-6 months at the maximum tolerated dose. Experts recommend a starting dose of 5 mg/kg/day, with a maximum daily dose of 20 mg/kg. Sensory neurotoxicity is a rare, dose limiting side effect of vitamin B-6.

- Oxlumo was the first FDA-approved medication indicated for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients. Oxlumo is an RNA interference therapy that reduces levels of the glycolate oxidase (GO) enzyme by targeting mRNA in the hepatocytes. Decreased GO enzyme levels reduce the amount of available glyoxylate, which is the substrate for oxolate production. The GO enzyme is upstream from the deficient AGT enzyme that causes PH1; therefore, the mechanism of action of Oxlumo is independent of the underlying AGXT gene mutation.

- The safety and efficacy of Rivfloza was established in the randomized, double-blind, placebo-controlled Phase II PHYOX2 trial which enrolled 35 patients aged 6 years or older with PH1 or PH2 and an eGFR ≥ 30 ml/min/1.73 m^2. Too few patients were enrolled to evaluate the efficacy in the PH2 population, therefore Rivfloza is only indicated for patients with PH1. Key exclusion criteria included prior kidney or liver transplantation, current or planned dialysis during the trial period, planed transplantation during the trial period, and use of an RNAi drug within the last 6 months.

    - Patients were randomized to receive monthly doses of Rivfloza (n=23) or placebo (n=12). The Rivfloza dose for patients at least 12 years of age weighing at least 50 kg was 160 mg, for patients at least 12 years of

age weighing less than 50 kg was 128 mg, and for children 6 to 11 years of age was 3.3 mg/kg (to a maximum of 128 mg).

- The primary endpoint was the area under the curve, from days 90 to 180, of the percent change in baseline in 24-hour urinary oxalate excretion (AUC24-hour Uox). The least-squares (LS) mean AUC24-hour Uox was -3486 in the Rivfloza group compared to +1490 in the placebo group, for a between group difference of 4976.

- The LS mean percent change from baseline in 24-hour urinary oxalate excretion averaged over days 90, 120, 150, and 180 was -37% in the Rivfloza group and 12% in the placebo group for a between group difference of 49%. Among patients with PH1, the between group difference was 56%.

- Clinical trials have shown that Oxlumo and Rivfloza can effectively treat the underlying pathophysiology of oxalate overproduction. Data to show that Oxlumo or Rivfloza delays or precludes the need for liver and/or kidney transplantation will impact these therapies prospective value.

    - Systemic oxalosis is defined as the spread of oxalate to organs outside of the kidneys, such as the joints, skin, bones, and heart. This can lead to organ dysfunction and death. One registry study found that around 40% of patients present with end-stage renal disease (ESRD) at the time of PH1 diagnosis, representing a significant proportion of the PH1 patient population.

    - In patients with PH1, aggressive hemodialysis is indicated once plasma oxalate levels exceed 30 mmol/L to prevent systemic oxalosis. Patients with PH1 and advanced renal disease carry a higher risk for systemic oxalosis, as renal excretion of oxalate is greatly reduced as eGFR declines, leading to an increase in plasma oxalate levels. Peritoneal dialysis alone does not achieve sufficient oxalate clearance; however, peritoneal dialysis in combination with hemodialysis may be necessary for those who do not respond to hemodialysis alone.

    - Dialysis is often used as a bridge to future liver and/or kidney transplantation in patients with PH1. Patients with a history of liver and/or kidney transplantation were excluded from all Oxlumo and Rivfloza trials, as removal of the patient's native liver is considered curative by removing the source of oxalate overproduction. Subsequent kidney transplantation or simultaneous liver-kidney transplantation may be required for those with ESRD. The role of transplantation in the setting of PH1 may change in the future with the introduction of small-interfering RNA therapies. However, additional long-term data is needed to understand whether these therapies can delay or eliminate the need for liver and/or kidney transplantation in patients with PH1.

References:

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<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.2</td><td>Effective Date: 02/12/2024</td><td>UM medical management system update for MAPPO and BCNA
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.1</td><td>Effective Date: 12/14/2023</td><td>New policy</td></tr>
<tr><td>1.0</td><td>Effective Date: 10/19/2023</td><td>UM medical management system update for BCBS and BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for **drugs covered under the medical benefit**. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	**Name**
ID Number	**Specialty**
D.O.B. ☐Male ☐Female	**Address**
Diagnosis	**City /State/Zip**
Drug Name	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**NPI**
Directions	**Contact Person**
Date of Service(s)	**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation *Date patient started therapy:* _____
2. Administered by patient or a medical professional? ☐ patient (self) ☐ health care professional (physician, nurse, etc.)
3. Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
   ☐ Hospital outpatient facility (go to #4) *Reason for Hospital Outpatient administration:* _____
   ☐ Hospital inpatient facility for Car-T therapy only (for example: Kymriah, Yescarta, or Tecartus) (go to #5)
4. Please specify location of administration if hospital outpatient infusion: _____
5. Please specify location of administration if hospital inpatient infusion: _____
6. Please provide the NPI number for the place of administration: _____
7. **Initiation AND Continuation of therapy:**
   a. What is the patient's diagnosis? _____
   b. What other medication has the patient received for their condition? Please list_____
      i. Please describe the response to previous therapies:
      _____
   c. Will the patient be receiving any other treatment for the listed condition while on this medication? Please list:
      _____
   d. Please list any labs values important for diagnosing or monitoring this patient's condition:
      _____
8. **Continuation of therapy:**
   a. Has the patient progressed while on this medication? ☐ yes ☐ no
   b. How has the patient's condition changed while on this medication?
      ☐ Improved: Please describe: _____
      ☐ Stable: please describe: _____
      ☐ Worsened; Please describe: _____
      ☐ Other; Please describe: _____

Chart notes are required for the processing of all requests. Please add any other supporting medical information necessary for our review **(required)**

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Provide chart notes	☐ Attach test results
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

7/26/2018, 9/18/2018; 1/31/2020; 3/17/2020; 8/9/2021