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: 12/12/2024

Oxlumo® (lumasiran)

HCPCS: J0224

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. Patient is not on peritoneal dialysis (PD)
   c. Patient does not have a history of kidney or liver transplant
   d. Trial and failure to at least 3 months, contraindication, OR intolerance to a course of high-dose vitamin B-6 therapy.
   e. Will not be used in combination with Rivfloza
   f. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

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:

- 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, causing 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.

- 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. 56% of patients in the clinical trials for Oxlumo received concomitant vitamin B-6. Sensory neurotoxicity is a rare, dose-limiting side effect of vitamin B-6.

- 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.

- Oxlumo is 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 approval of Oxlumo was based on three studies in patients with PH1: a randomized control trial in pediatric patients ages 6 years and older with PH1 (ILLUMINATE-A), a single-arm clinical trial in pediatric patients less than 6 years of age with PH1 (ILLUMINATE-B), and a single-arm clinical trial in pediatric and adult patients with PH1 with advanced chronic kidney disease, including those on hemodialysis (ILLUMINATE-C). Of note, the ILLUMINATE-A and ILLUMINATE-B trials excluded patients with systemic oxalosis, eGFR <30-45 mL/min, undergoing dialysis, or a history of kidney and liver transplants. ILLUMINATE-C did not exclude patients with eGFR <30 mL/min or those undergoing hemodialysis, and trial results support the efficacy of Oxlumo in PH1 patients with advanced renal disease. Of note, patients undergoing peritoneal dialysis and those with history of kidney or liver transplants were excluded from ILLUMINATE-C.

    - The first trial, ILLUMINATE-A, was a placebo-controlled, double blind randomized controlled trial including patients 6 to 61 years old. 26 patients received Oxlumo and 13 received placebo. The primary endpoint was percent reduction from baseline in 24-hour urinary oxalate excretion (corrected for BSA) in months 3 to 6 of the trial. The least squares mean percent change was -65% (95% CI: -71, -59) in the Oxlumo group and -12% (95% CI: -20, -4) in the placebo group. By 6 months, 52% of patients receiving Oxlumo achieved normal 24-hour urinary oxalate, compared to 0% of patients receiving placebo.

- The second trial, ILLUMINATE-B, was a single-arm study. 16 patients younger than six years of age received Oxlumo. Using another measure of oxalate in the urine, the study showed, on average, a 71% (95% CI: 65, 77) decrease in urinary oxalate by the sixth month of the study.

- The third trial, ILLUMINATE-C, was a single-arm study that assessed the efficacy of Oxlumo in patients with PH1 with advanced renal disease (eGFR <30mL/min or those receiving hemodialysis). 21 patients aged 0 months and older (range: 0-59 years) received Oxlumo. Using the measure of oxalate in the plasma, the study showed on average a 33% (95% CI: -15, 82) and 42% (95% CI: 34, 51) reduction in plasma oxalate at month 6 compared to baseline, respectively, for patients not receiving hemodialysis at enrollment (Cohort A, N=6) and for patients receiving hemodialysis at enrollment (Cohort B, N=15). Additionally, at 6 months, no patients demonstrated worsening of nephrocalcinosis grade, 2 patients demonstrated no change in nephrocalcinosis grade, and 5 patients demonstrated improvement in nephrocalcinosis grade compared to baseline.

- Rivfloza™ is the 2nd FDA approved medication for the treatment of PH1. 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. In addition, Rivfloza is approved for both self-administration and healthcare provider administration.

- Clinical trials showed 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 is forthcoming and 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. The ILLUMINATE-C trial established the efficacy of Oxlumo in patients with advanced PH1, including those with systemic oxalosis and those undergoing hemodialysis. 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. Patients receiving peritoneal dialysis either alone or in combination with hemodialysis were excluded from ILLUMINATE-C.

    - 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 such as Oxlumo. However, additional long-term data is needed to understand whether Oxlumo can delay or eliminate the need for liver and/or kidney transplantation in patients with PH1.

- No studies have been done using Oxlumo and Rivfloza in combination. Patients were excluded from the Rivfloza PHYOX2 clinical trial if they had use of an RNAi drug within the last 6 months.

References:

1. Oxlumo [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals; September 2003.
2. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. N Engl J Med. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712
3. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: A new RNAi therapeutic in infants and young children. Genet Med. 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024
4. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial [published online ahead of print, 2022 Jul 14]. Am J Kidney Dis. 2022;S0272-6386(22)00771-5. doi:10.1053/j.ajkd.2022.05.012
5. Drug manufacturer press release. Available at: https://www.businesswire.com/news/home/20201124005407/en/Alnylam-Announces-U.S.-Food-and-Drug-Administration-FDA-Approval-of-OXLUMO%E2%84%A2-lumasiran-the-First-and-Only-Treatment-Approved-for-Primary-Hyperoxaluria-Type-1-to-Lower-Urinary-Oxalate-Levels-in-Pediatric-and-Adult-Patients. Accessed on November 24, 2020.
6. IPD Analytics. Oxlumo (lumasiran) New Drug Review. Published December 2020. Accessed December 10, 2020.
7. Danpure CJ. Molecular etiology of primary hyperoxaluria type 1: new directions for treatment. Am J Nephrol. 2005;25(3):303-310. doi:10.1159/000086362
8. Strauss SB, Waltuch T, Bivin W, Kaskel F, Levin TL. Primary hyperoxaluria: spectrum of clinical and imaging findings. Pediatr Radiol. 2017;47(1):96-103. doi:10.1007/s00247-016-3723-7
9. Niaudet, P. Treatment of Primary Hyperoxaluria Type 1. UpToDate. Available at: https://www.uptodate.com/contents/primary-hyperoxaluria#H3. Accessed on January 4, 2022
10. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. 2009;75(12):1264-1271. doi:10.1038/ki.2009.32
11. Hoyer-Kuhn H, Kohbrok S, Volland R, et al. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol. 2014;9(3):468-477. doi:10.2215/CJN.06820613
12. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27(5):1729-1736. doi:10.1093/ndt/gfs078
13. Rivfloza [prescribing information]. Plainsboro, NJ. Novo Nordisk Inc. September 2023.
14. Baum MA, Langman C, Cochat P, Lieske JC, Moochhala SH, Hamamoto S, Satoh H, Mourani C, Ariceta G, Torres A, Wolley M, Belostotsky V, Forbes TA, Groothoff J, Hayes W, Tönshoff B, Takayama T, Rosskamp R, Russell K, Zhou J, Amrite A, Hoppe B; PHYOX2 study investigators. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. Kidney Int. 2023 Jan;103(1):207-217. doi: 10.1016/j.kint.2022.07.025. Epub 2022 Aug 22. PMID: 36007597

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.8</td><td>Effective Date: 12/12/2024</td><td>Annual review completed, no changes to criteria</td></tr>
<tr><td>1.7</td><td>Effective Date: 12/14/2023</td><td>Updated to remove prescriber requirements and add criteria to not allow for use of Oxlumo in combination with Rivfloza</td></tr>
<tr><td>1.6</td><td>Effective Date: 06/08/2023</td><td>Hyperhydration criterion removed for patients based on ILLUMINATE-C study results</td></tr>
<tr><td>1.5</td><td>Effective Date: 12/01/2022</td><td>Criteria updated to reflect Oxlumo’s expanded indication to lower plasma oxalate levels in patients with advanced renal disease:
Removed criteria requiring eGFR >30
Revised criteria to exclude only those receiving peritoneal dialysis based on exclusion criteria in ILLUMINATE-C
Removed criteria requiring no clinical evidence of systemic oxalosis</td></tr>
<tr><td>1.4</td><td>Effective Date: 02/10/2022</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 6/22/2021</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>1.2</td><td>Effective Date: 03/01/2021</td><td>UM medical management system update for BCBSM
<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>
<tr><td>1.1</td><td>Effective Date: 02/05/2021</td><td>UM medical management system update for BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</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>
<tr><td>1.0</td><td>Effective Date: 02/04/2021</td><td>New Policy</td></tr>
</table>

** 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.*