Policy Number	**RX501.133**
Policy Effective Date	**09/15/2024**
Policy End Date	**12/31/2025**

Lumasiran

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Lumasiran (Oxlumo™) **may be considered medically necessary** when **ALL** of the following criteria are met:

- Diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by ONE of the following:
  a. Genetic testing demonstrating AGXT gene mutation; or
  b. Liver biopsy demonstrating alanine: glyoxylate aminotransferase (AGT) deficiency; **AND**
- Presence of ONE of the following:
  a. Elevated urinary oxalate level (≥ 0.7 mmol/24 hr/1.73 m^2); or
  b. Increased urinary oxalate: creatinine ratio (e.g., relative to normative values for age); or
  c. Increased plasma oxalate concentration (e.g., greater than the upper limit of normal); **AND**
- Documented failure, inadequate response, contraindication, or intolerance to treatment with vitamin B6 (pyridoxine); **AND**
- Will NOT use lumasiran concurrently with other biologics used to treat primary hyperoxaluria (e.g., nedosiran); **AND**
- Individual does not have a history of liver transplantation.

Lumasiran (Oxlumo™) **is considered experimental, investigational and/or unproven** in all other situations.

Policy Guidelines

None.

Description

Primary Hyperoxaluria

Primary hyperoxaluria is a group of rare autosomal recessive genetic metabolic disorders that are characterized by the accumulation of oxalate in the kidneys and other organs in the body. (1) Primary hyperoxaluria type 1 (PH1) is the most severe and most common of the three types of primary hyperoxaluria and accounts for approximately 70 to 80% of patients with primary hyperoxaluria. The estimated prevalence of PH1 in the United States is approximately 1 to 3 cases per million individuals. (2)

PH1 is caused by mutations in the AGXT gene that result in deficient or absent activity of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT), which normally

converts glyoxylate to glycine. (1) Deficient levels of the AGT enzyme ultimately leads to the overproduction of oxalate in the body. Excess oxalate begins to accumulate in kidney tissue in the form of calcium oxalate crystals and can lead to progressive kidney damage and kidney failure.

Kidney stones are commonly the first sign of hyperoxaluria and can cause a variety of symptoms such as sudden abdominal or flank pain; blood in the urine; frequent urge to urinate; and pain while urinating. (1) Signs and symptoms of PH1 vary in severity and may begin anytime from infancy to adulthood. The median age of onset of symptoms is about 5.5 years. (3)

Treatment

Lumasiran

Lumasiran (Oxlumo) works by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference, which leads to reduced levels of glycolate oxidase (GO) enzyme. (4) Decreased GO enzyme levels reduce the amount of available glyoxylate, which is a substrate for oxalate production.

The recommended dose for Oxlumo is based on actual body weight and is administered by a healthcare professional as a subcutaneous injection. (4) The recommended weight-based regimen consists of three loading doses, followed by maintenance doses, as shown in Table 1.

Table 1. Oxlumo Weight-Based Dosing Regimen (4)

Body Weight	**Loading Dose**	**Maintenance Dose (begin 1 month after the last loading dose)**
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

kg: kilogram; mg: milligram

Regulatory Status

On November 23, 2020, Oxlumo™ (lumasiran) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients. (4)

Rationale

This policy was created in February 2021 and is based in part on the U.S. Food and Drug Administration (FDA) approved indication for Oxluma™ (lumasiran). The FDA based their approval on the evidence from three phase 3 studies (ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C). (4)

ILLUMINATE-A

ILLUMINATE-A was a randomized, double-blind trial comparing lumasiran and placebo in 39 patients 6 years of age and older with primary hyperoxaluria type 1 (PH1) and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 (ILLUMINATE-A; NCT03681184). Patients received 3 loading doses of 3 mg/kg Oxlumo (N=26) or placebo (N=13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg Oxlumo or placebo. After 6 months, all patients received Oxlumo. (4)

The median age of patients at first dose was 15 years (range 6 to 61 years), 67% were male, and 77% were White. At baseline, the median 24-hour urinary oxalate excretion corrected for body surface area (BSA) was 1.7 mmol/24 h/1.73 m^2, the median plasma oxalate level was 13.1 µmol/L, 33% of patients had eGFR ≥90 mL/min/1.73 m^2, 49% had eGFR of 60 to <90 mL/min/1.73 m^2, and 18% had eGFR 30 to <60 mL/min/1.73 m^2, 56% were on pyridoxine, and 85% reported a history of symptomatic kidney stone events. (4)

The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over Months 3 through 6. The least square (LS) mean percent change from baseline in 24-hour urinary oxalate in the Oxlumo group was -65% (95% CI: -71, -59) compared with -12% (95% CI: -20, -4) in the placebo group, resulting in a between-group LS mean difference of 53% (95% CI: 45, 62; p<0.0001). (4)

By Month 6, 52% (95% CI: 31, 72) of patients treated with Oxlumo achieved a normal 24-hour urinary oxalate corrected for BSA (≤0.514 mmol/24 hr/1.73 m^2) compared to 0% (95% CI: 0, 25) placebo-treated patients (p=0.001). Reduced urinary oxalate levels were maintained through Month 24 in patients treated with Oxlumo. (4)

ILLUMINATE-B

ILLUMINATE-B was a single-arm study in 18 patients <6 years of age with PH1 and an eGFR >45 mL/min/1.73 m^2 for patients ≥12 months of age or a normal serum creatinine for patients <12 months of age (ILLUMINATE-B; NCT03905694). Dosing was based on body weight. (4)

The median age of patients at first dose was 51 months (range 4 to 74 months), 56% were female, and 88% were White. Three patients were less than 10 kg, 12 were 10 kg to < 20 kg, and 3 were ≥ 20 kg. The median spot urinary oxalate:creatinine ratio at baseline was 0.47 mmol/mmol. (4)

The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over Months 3 through 6. Patients treated with Oxlumo achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 72% (95% CI: 66, 78). The reduction in urinary oxalate excretion was maintained with continued Oxlumo treatment through Month 12. (4)

ILLUMINATE-C

A total of 21 patients were enrolled and treated with Oxlumo in a multi-center, single-arm study in patients with PH1 and an eGFR ≤ 45 mL/min/1.73 m^2 in patients 12 months of age and older or an elevated serum creatinine for age in patients less than 12 months of age, including patients on hemodialysis. ILLUMINATE-C included 2 cohorts. Cohort A included 6 patients who did not require dialysis at the time of study enrollment. Cohort B included 15 patients who were on a stable regimen of hemodialysis; the hemodialysis regimen was to remain stable in these patients for the first 6 months of the study. Patients received the recommended dosing regimen of Oxlumo based on body weight. Patients requiring peritoneal dialysis were excluded.

The median age of patients at first dose was 9 years (range 0 to 59 years), 57% were male, and 76% were White. For Cohort A, the median plasma oxalate level was 58 µmol/L. For Cohort B, the median pre-dialysis plasma oxalate level was 104 µmol/L.

The primary endpoint was the percent change in plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort A (N = 6) and the percent change in pre-dialysis plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort B (N = 15). The percent change from baseline to Month 6 in plasma oxalate levels in Cohort A was an LS mean difference of -33% (95% CI: -82, 15) and in Cohort B was -42% (95% CI: -51, -34).

Mean plasma oxalate decreased from 65 µmol/L (95% CI: 21, 108) at baseline to 33 µmol/L (95% CI: 10, 56) at Month 6 in Cohort A, and from 108 µmol/L (95% CI: 92, 125) at baseline to 62 µmol/L (95% CI: 51, 72) at Month 6 in Cohort B. (4)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0224

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. National Organization for Rare Disorders. Primary Hyperoxaluria (2024). Available at <https://rarediseases.org> (accessed July 30, 2024).

2. Shah A, Leslie SW, Ramakrishnan S. Hyperoxaluria. [Updated March 4, 2024]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2024. Available at <https://www.ncbi.nlm.nih.gov> (accessed July 30, 2024).
3. Lieske JC, Monico CG, Holmes WS, et al. International registry for primary hyperoxaluria. Am J Nephrol. May-June 2005; 25(3):290-296. PMID 15961949
4. Food and Drug Administration (FDA) Prescribing Label. Oxlumo™ (lumasiran) (September 2023). Available at <https://www.accessdata.fda.gov> (accessed July 30, 2024).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Revised conditional coverage to remove "and potassium citrate or sodium citrate" from "Documented failure, inadequate response, contraindication, or intolerance to treatment with vitamin B6 (pyridoxine);" and 2) Removed "history of kidney transplantation or estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m^2." References updated.
05/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Updated conditional coverage adding: "Documented failure, inadequate response, contraindication or intolerance to treatment with vitamin B6 (pyridoxine) AND potassium citrate or sodium citrate; **AND** Will NOT use lumasiran concurrently with other biologics used to treat primary hyperoxaluria (e.g., nedosiran); **AND"**; and 2) Updated urinary oxalate level from "greater than 1 mmol/1.73 m2 per day [90 mg/1.73 m2 per day]" to "≥ 0.7 mmol/24 hr/1.73 m^2**".** References updated.
10/15/2022	Reviewed. No changes.
08/01/2021	New medical document. Lumasiran (Oxlumo™) may be considered medically necessary for the diagnosis of primary hyperoxaluria type 1 (PH1) when conditional criteria are met.