Original Effective Date: 05/01/2021
Current Effective Date: 10/09/2024
Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
Policy Number: C21126-A

Oxlumo (lumasiran)

PRODUCTS AFFECTED

Oxlumo (lumasiran)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Primary hyperoxaluria type1 (PH1)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PRIMARY HYPEROXALURIA TYPE 1 (PH1):
1. Documented diagnosis of Primary hyperoxaluria type 1
   NOTE: Oxlumo is not effective in primary hyperoxaluria type 2 (PH2) or type 3 (PH3) because

its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2 and PH3
AND

2. Documentation diagnosis confirmed by alanine-glyoxylate aminotransferase (AGXT) gene mutation OR Liver biopsy demonstrating significantly decreased or absent alanine: glyoxylate aminotransferase (AGT) enzyme activity [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests member has made efforts to increase fluid intake to at least 3 L/1.73 m2 per day
   AND
4. Documentation of concurrent use of pyridoxine or trial and failure of or serious side effects to pyridoxine for at least 3 months with no significant improvement observed (e.g., <30% reduction in urine oxalate concentration after at least 3 months of therapy.)
   AND
5. Prescriber attests or clinical reviewer has found the member does not require peritoneal dialysis and that the member has not had previous kidney or liver transplant
   AND
6. Laboratory documentation of member's baseline urinary oxalate level [DOCUMENTATION REQUIRED]
   OR
   IF REDUCED RENAL FUNCTION: Laboratory documentation of member's baseline plasma oxalate level [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:

A. PRIMARY HYPEROXALURIA TYPE 1 (PH1):

1. Prescriber attests to or clinical review has found no evidence of disease progression or unacceptable toxicity
   AND
2. Documentation of laboratory improvement or stabilization in urinary oxalate excretion or plasma oxalate from baseline. (Consideration for improvement as reaching near normal [< 1 mmol/1.73m^2 per day] urinary oxalate excretion. Consideration for improvement is decreasing plasma oxalate level.) [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests or clinical reviewer has found the member does not require peritoneal dialysis and that the member has not had previous kidney or liver transplant

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy:12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a nephrologist, urologist or geneticist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

No restriction

QUANTITY:

Body Weight	Loading Dose	Maintenance Dose
Less than 10 kg	6 mg/kg once monthly x 3 doses	3 mg/kg once monthly
10 kg to < 20 kg	6 mg/kg once monthly x 3 doses	6 mg/kg once every 3 months
20 kg and above	3 mg/kg once monthly x 3 doses	3 mg/kg once every 3 months

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Sit of Care program.

Note: Site of Care Utilization Management Policy applies for Oxlumo (lumasiran). For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Small Interfering Ribonucleic Acid Agents (siRNA)

FDA-APPROVED USES:
Indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Oxlumo (lumasiran) is the first agent approved by the Food and Drug Administration (FDA) for the treatment for primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in adult and pediatric individuals.
Primary hyperoxaluria is a rare inherited error of glyoxylate metabolism characterized by an excess production of oxalate. The excess oxalate is excreted by the kidneys, typically at a rate greater than 1 mmol/1.73 m2 per day (normal is less than 0.5 mmol/1.73 m2 per day). Increased urinary excretion of oxalate leads to urolithiasis and nephrocalcinosis. Progressive disease can result in end-stage kidney disease and systemic oxalate deposition.
Primary hyperoxaluria (PH) is divided into three primary types, each caused by a mutation in a gene that encodes an enzyme that plays a role in glyoxylate metabolism. PH1 is the most common type, accounting for approximately 80% of PH cases. PH1 is caused by mutation in the AGXT gene which leads to decreased activity of the hepatic alanine: glyoxylate aminotransferase (AGT) enzyme. PH2 accounts for 10% of cases and is caused by mutation in the GRHPR gene, leading to decreased activity of the glyoxylate reductase/hydroxypyruvate reductase (GRHPR) enzyme. PH3 accounts for 5% of cases and is caused by mutation in the HOGA1 gene that encodes the mitochondrial 4- hydroxy-2-oxoglutarate aldolase enzyme. In individuals with increased urinary oxalate excretion, diagnosis is confirmed by genetic testing or liver biopsy showing decreased or absent enzyme activity.
Conservative management of PH1 should include high fluid intake (greater than 3 liters/1.73 m2 per day) to reduce oxalate deposition in the kidneys. Neutral phosphate (orthophosphate), potassium citrate-citric acid and/or magnesium oxide can also be beneficial to prevent urinary oxalate precipitation. Pyridoxine is

a coenzyme of AGT that promotes the conversion of glyoxylate to glycine instead of oxalate. Up to 30% of individuals with PH1 experience a significant reduction in hyperoxaluria in response to pyridoxine therapy. A three to six-month trial of pyridoxine at a dose between 5 and 20 mg/kg per day is prudent in all individuals with PH1.

Oxlumo treats PH1 by decreasing levels of the glycolate oxidase (GO) enzyme in the liver, thereby reducing a substrate necessary for oxalate production. The GO enzyme is upstream of AGT, the enzyme that is deficient in PH1. Oxlumo is only expected to be effective in PH1 as it does not impact the metabolic pathways leading to hyperoxaluria in PH2 and PH3.

The clinical efficacy of Oxlumo was demonstrated in the ILLUMINATE clinical trial program. ILLUMINATE- A was a randomized, double blind, placebo-controlled trial in 39 individuals 6 years of age and older with PH1 and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2. Individuals with a history of renal or liver transplant were excluded. The primary endpoint was the percent reduction in urinary oxalate excretion averaged over months 3 through 6. The mean percent change from baseline in urinary oxalate in the Oxlumo group was -65% compared with -12% in the placebo group ($p<0.0001$).

ILLUMINATE-B was a single-arm study in 18 individuals less than 6 years of age with PH1 and preserved renal function. Individuals with a history of renal or liver transplant were excluded. The primary endpoint was the percent reduction in spot urinary oxalate: creatinine ratio averaged over months 3 through 6. Individuals treated with Oxlumo demonstrated a reduction in spot urinary oxalate: creatinine ratio from baseline of 71%.

ILLUMINATE-C was a single-arm study in 21 individuals with advanced PH1, including individuals with severe renal impairment and those on dialysis. 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 hemodialysis. The primary endpoint was the percent change in plasma oxalate from baseline to Month 6 for Cohort A (N = 6) and the percent change in pre-dialysis plasma oxalate from baseline 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.
Patients of all ages with advanced PH1 had substantial reductions in POx after receiving 6 months of lumasiran treatment, with encouraging early results on measures of systemic oxalosis and a generally acceptable safety profile. The most commonly reported lumasiran-related AEs were injection-site reactions. These results, along with previous reports from ILLUMINATE-A and ILLUMINATE-B, provide evidence supporting the effectiveness and safety of lumasiran across the full spectrum of disease severity in PH1.

The dosing schedule is based on actual body weight and includes three monthly loading doses followed by maintenance doses either monthly or every 3 months

Currently, there are no other FDA-approved treatments for PH1. Conservative management includes increasing fluid intake to 3 L/m2 BSA per day to create a high urinary output following diagnosis; this is the most effective therapy to decrease tubular fluid oxalate concentration and intratubular oxalate deposition. In addition, pyridoxine should be tried for at least 3 months in all patients with PH1, as those who respond to therapy see a significant reduction in urinary oxalate excretion that is maintained for years.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Oxlumo (lumasiran) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Oxlumo (lumasiran) include: No

labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
Oxlumo is intended for subcutaneous administration by a healthcare professional.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0224	Injection, lumasiran, 0.5 mg

AVAILABLE DOSAGE FORMS:
Oxlumo SOLN 94.5MG/0.5ML single-dose vial

REFERENCES

1. Oxlumo (lumasiran) injection, for subcutaneous use [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals; September 2023.
2. Genetic and Rare Diseases Information Center. Primary hyperoxaluria type 1. https://rarediseases.info.nih.gov/diseases/2835/primary-hyperoxaluria-type-1 Updated November 8, 2021. Accessed May 2022.
3. National Institutes of Health. In NIH trial, A Study to Evaluate Lumasiran in Children andAdults with Primary Hyperoxaluria Type 1 (ILLUMINATE-A, NCT03681184). www.clinicaltrials.gov. Published September 2018. Updated January 2021.
4. National Institutes of Health. In NIH trial, A Study to Evaluate Lumasiran in Infants andYoung Children with Primary Hyperoxaluria Type 1 (ILLUMINATE-B, NCT03905694). www.clinicaltrials.gov. Published April 2019. Updated January 2021.
5. National Institutes of Health. In NIH trial, A Study to Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C, NCT04152200). www.clinicaltrials.gov. Published November 2019. Updated January 2021.
6. National Institutes of Health. In NIH trial, Long Term Extension Study in Patients with Primary Hyperoxaluria (PHYOX3, NTC04042402). www.clinicaltrials.gov. Published August 2019. Updated February 2021.
7. Bhasin B, Urekli HM, Atta MG. Primary and secondary hyperoxaluria: understanding the enigma. World J Nephrol. 2015;4(2):235-244. doi:10.5527/wjn.v4.i2.235
8. Milliner, D. S., Cochat, P., Hulton, S.-A., Jérôme Harambat, Baños, A., Dehmel, B., & Lindner, E. (2021). Plasma oxalate and eGFR are correlated in primary hyperoxaluria patients with maintained kidney function—data from three placebo-controlled studies. Pediatric Nephrology, 36(7), 1785–1793. https://doi.org/10.1007/s00467-020-04894-9
9. Michael, M., Groothoff, J. W., Shasha-Lavsky, H., Lieske, J. C., Frishberg, Y., Simkova, E., … Magen, D. (2023). Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial. American Journal of Kidney Diseases, 81(2), 145-155.e1. https://doi.org/10.1053/j.ajkd.2022.05.012

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information References	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Drug Class FDA-Approved Background Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file