Medical Drug Clinical Criteria

Subject:	Oxlumo (lumasiran)		
Document #:	CC-0185	**Publish Date:**	02/03/2025
Status:	Revised	**Last Review Date:**	12/09/2024

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Overview

This document addresses the use of Oxlumo (lumasiran), a *HAO1*-directed small interfering ribonucleic acid (siRNA) approved by the Food and Drug Administration (FDA) for the treatment for primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in adult and pediatric individuals. Oxlumo is intended for subcutaneous administration by a healthcare professional. 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.

Primary hyperoxaluria (PH) is divided into three 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 m^2 per day) to reduce oxalate deposition in the kidneys. Alkalinization of urine 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. 30-50% of individuals with PH1 experience a significant reduction in hyperoxaluria in response to pyridoxine therapy. A trial of pyridoxine at a dose between 5 and 20 mg/kg per day is prudent in individuals with a pyridoxine-responsive genotype.

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 m^2. 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 PH1 and advanced kidney disease. Cohort A included 6 individuals who did not require dialysis at enrollment and cohort B included 15 individuals who were on a stable regimen of hemodialysis. The primary endpoint was the percent change in plasma oxalate averaged over months 3 through 6. Individuals treated with Oxlumo demonstrated a mean difference in plasma oxalate levels of -33% in cohort A and -42% in cohort B.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Oxlumo (lumasiran)

Initial requests for Oxlumo (lumasiran) may be approved if the following criteria are met:

I. Individual has a diagnosis of primary hyperoxaluria type 1 (PH1); **AND**
II. Documentation is provided that diagnosis has been verified by (Cochat 2012; Milliner 2022):
    A. Genetic testing demonstrating mutation in the alanine:glyoxylate aminotransferase (*AGXT)* gene; **OR**
    B. Liver biopsy demonstrating significantly decreased or absent alanine:glyoxylate aminotransferase (AGT) enzyme activity; **AND**
III. Documentation is provided that individual has elevated urinary oxalate levels or plasma oxalate levels; **AND**
IV. Individual is using in combination with pyridoxine (unless individual is a pyridoxine non-responder) (Cochat 2012; Milliner 2022).

Continuation requests for Oxlumo (lumasiran) may be approved if the following criteria are met:

I. Individual has a diagnosis of primary hyperoxaluria type 1 (PH1); **AND**
II. Documentation is provided that diagnosis has been verified by (Cochat 2012; Milliner 2024):
    A. Genetic testing demonstrating mutation in the alanine:glyoxylate aminotransferase (AGXT) gene; **OR**
    B. Liver biopsy demonstrating significantly decreased or absent alanine:glyoxylate aminotransferase (AGT) enzyme activity; **AND**
III. Documentation is provided that there is clinically significant reduction in urinary oxalate excretion, spot urinary oxalate:creatinine ratio or plasma oxalate levels) with Oxlumo therapy; **AND**
IV. Individual is using in combination with pyridoxine (unless individual is a pyridoxine non-responder) (Cochat 2012; Milliner 2024).

Oxlumo (lumasiran) may not be approved for the following:

I. Individual with primary hyperoxaluria type 2 or type 3; **OR**
II. Individual with a history of or planned kidney or liver transplant (NCT 03681184, NCT 03905694, NCT 04152200); **OR**
III. Use in combination with Rivfloza (nedosiran); **OR**
IV. May not be approved when the above criteria are not met and for all other indications.

Initial Approval Duration: 6 months
Continuation Approval Duration: 1 year

Quantity Limits

Oxlumo (lumasiran) Quantity Limit

Drug	Body Weight	Loading Dose	Maintenance Dose (starting one month after the last loading dose)
Oxlumo (lumasiran) 94.5 mg/0.5 mL vial	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
	20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0224	Injection, lumasiran, 0.5 mg [Oxlumo]

ICD-10 Diagnosis

E72.53	Primary hyperoxaluria

Document History

Revised: 12/9/2024
Document History:

- 12/9/2024 – Annual Review: Add diagnosis criteria to continuation criteria. Administrative update to add documentation. Wording and formatting updates. Coding Reviewed: No changes.
- 5/17/2024 – Select Review: No changes. Coding Reviewed: No changes.
- 12/11/2023 – Annual Review: Revise oxalate level criteria and transplant may not approve criteria; add may not approve criteria for combination with Rivfloza. Wording and formatting changes. Coding Reviewed: No changes.
- 12/12/2022 – Annual Review: Update clinical criteria by removing fluid intake criteria; add additional endpoints to continuation criteria; remove renal impairment from may not approve criteria. Update references. Wording and formatting changes. Coding Reviewed: No changes.
- 12/13/2021 – Annual Review: Wording and formatting changes. Administrative update to add documentation. Coding Reviewed: No changes.
- 12/14/2020 – Annual Review: Add new criteria and quantity limit for Oxlumo. Coding Reviewed: Added HCPCS J3490, C9074. Added ICD-0-CM E72.53. All diagnosis pend for NOC codes. Effective 7/1/2021 Added HCPCS J0224. Removed J3490 and C9074. Delete All diagnosis pend.

References

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2. Alnylam Pharmaceuticals. A study to evaluate lumasiran in children and adults in primary hyperoxaluria type 1 (ILLUMINATE-A). NLM Identifier: NCT 03681184. Last updated: August 12, 2024. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03681184?term=03681184&draw=2&rank=1. Accessed: December 5, 2024.
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