Subject:	Oxlumo (lumasiran)		
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Overview

This document addresses the use of Oxlumo (lumasiran), 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 m^2 per day (normal is less than 0.5 mmol/1.73 m^2 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 m^2 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 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 is an ongoing clinical trial in individuals with advanced PH1, including individuals with severe renal impairment and those on dialysis.

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.

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 ~~D~~diagnosis has been confirmed by (Cochat 2012; Milliner 2005):
    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. Individual is using in combination with high fluid intake (at least 3 liters/1.73 m^2 per day) (Cochat 2012; Hoppe 2009); **AND**
IV. Individual is using in combination with pyridoxine **OR** individual has had a trial and inadequate response to pyridoxine (Cochat 2012; Hoppe 2009).

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

I. Documentation is provided that ~~T~~there is ~~confirmation of~~ clinically significant reduction in urinary oxalate excretion; **AND**
II. Individual is using in combination with high fluid intake and pyridoxine (unless individual is a pyridoxine non-responder) (Cochat 2012; Hoppe 2009).

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

I. All other indications not included above; **OR**
II. Individual with primary hyperoxaluria type 2 or type 3; **OR**
III. Individual with a history of renal or liver transplant (NCT 03681184, NCT 03905694); **OR**
IV. Indivdiual has an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2 (NCT 03681184, NCT 03905694).

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: 12/13/2021
Document History:

- 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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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.