Drug Monograph

Drug Name: **Oxlumo™ (lumasiran) vial**
Drug Class: **RNAi Targeting of Glycolate Oxidase (GO)**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Oxlumo is available as a single-dose vial containing 94.5mg/0.5ml of lumasiran.
Manufacturer:	Distributed by: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142.
Summary of Findings:	The efficacy of Oxlumo was established in two clinical trials. ILLUMINATE-A was a double-blind, placebo controlled Phase 3 trial of 39 patients 6 years of age or older with primary hyperoxaluria type 1 (PH1) and an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2. Primary endpoint was the percent reduction in 24-hour urinary oxalate excretion corrected for body surface area (BSA) averaged over months 3 through 6. In the treatment group there was a 65% reduction versus 12% in the placebo group. The ILLUMINATE-B study was a single-arm study in patients under 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. The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months 3 through 6. Efficacy analysis included the first 16 patients who received 6 months of treatment with Oxlumo. There was a 71% percent reduction from baseline in those patients.

Status Recommendation:	☒ Clinical Edit ☐ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2,3]

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder (2q) in which a mutation in the AGXT gene causes a defect in the liver peroxisomal enzyme, alanine-glyoxylate aminotransferase (AGT) which leads to an overproduction of oxalate combining with calcium to form insoluble crystals. This leads to urolithiasis, nephrocalcinosis and kidney failure. The course of this disease leads to the damage of multiple organs due to systemic oxalosis. Additional subtypes, primary hyperoxaluria type 2 (PH2) and primary hyperoxaluria type 3 (PH3), are caused by mutations in other genes. Oxlumo is not expected to be effective in PH2 or PH3 because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in those subtypes. PH1 is the most common and severe type of PH and accounts for approximately 80% of all PH cases. Patients typically develop recurrent kidney stones with progressive nephrocalcinosis and end stage renal disease by 20 to 30 years of age. Among patients with PH, about 50% will have kidney failure by age 15, and about 80% will have kidney failure by age 30. It is estimated that the prevalence of PH1 is approximately 1 to 3 per million people in North America. This may be an underestimate because of the high probability of misdiagnosis or being undiagnosed.

Dosage Form [4]

Oxlumo is available as a single-dose vial containing 94.5mg/0.5ml of lumasiran.

Manufacturer [4]

Distributed by: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142.

Indication(s) [4]

Oxlumo is indicated for the treatment of PH1 to lower urinary oxalate levels in pediatric (as young as 3 months of age) and adult patients.

Clinical Efficacy [4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Oxlumo reduces levels of glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production. As the GO enzyme is upstream of the deficient alanine:glyoxylate aminotransferase (AGT) enzyme that causes PH1, the mechanism of action of Oxlumo is independent of the underlying *AGXT* gene mutation.

Pharmacokinetics:

Absorption	T_{max}= 4 hours
Metabolism	By endo- and exonucleases to oligonucleosides of shorter lengths
Excretion	Urine: < 26% in 24 hours, with the rest as inactive metabolite
Half-life	5.2 hours

Clinical Trials Experience:

STUDY 1 DESIGN (ILLUMINATE-A)	Phase 3 randomized, double-blind placebo controlled trial (n=39)
INCLUSION CRITERIA	• Six years of age or older • eGFR ≥30 ml/min/1.73 m^2 • Confirmed PH1 disease • If taking Vitamin B_6 (pyroxidine), must have been on a stable regimen for at least 90 days
EXCLUSION CRITERIA	• Clinically significant health concerns or clinical evidence of extrarenal systemic oxalosis • Clinically significant abnormal laboratory results • Known active or evidence of HIV or hepatitis B or C infection • eGFR of <30 ml/min/1.73 m^2 at screening • Received an investigational agent within 30 days or 5 half-lives before the first dose of study drug or are in follow-up of another clinical study • History of kidney or liver transplant • Known history of multiple drug allergies or allergic reaction to an oligonucleotide of GaINAc • History of intolerance to subcutaneous injection • Women who are pregnant, planning pregnancy, or breast-feeding or those of child bearing potential and not willing to use contraception • History of alcohol abuse within the last 12 months, or unable or unwilling to limit alcohol consumption throughout the study
TREATMENT REGIMEN	Three loading doses of 3 mg/kg administered monthly followed by quarterly maintenance doses of 3 mg/kg, to placebo.
RESULTS	The primary endpoint was the percent reduction from baseline in 24-hours urinary oxalate excretion corrected for BSA averaged over months 3 through 6. The primary endpoint analysis demonstrated a significant reduction (p<0.0001) in urinary oxalate excretion in the Oxlumo group versus placebo. The percent reduction was 65% (95% CI: -71, -59) and 12% (95% CI: -20, -4) for the Oxlumo and placebo groups, respectively. The group LS mean difference was 53% (95% CI: 45, 62). Secondary Endpoint: 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).
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN (ILLUMINATE-B)	Phase 3, six-month, single-arm study with dosing based on body weight (n=16)

INCLUSION CRITERIA	• Patients <6 years of age
	  ○ eGFR >45 mL/min/1.73 m^2 for patients ≥12 months of age
	  ○ Normal serum creatinine for patients <12 months of age
	• Has confirmation of PH1
	• Meets urinary oxalate excretion requirements
	• If taking Vitamin B_6 (pyroxidine), must have been on a stable regimen for at least 90 days

EXCLUSION CRITERIA	• Abnormal serum creatinine levels at screening for infants who are less than 1 year old • Does not have relatively preserved kidney function • Clinical evidence of systemic oxalosis • History of kidney or liver transplant
TREATMENT REGIMEN	Treatment was based on body weight according to the chart in Dosing and Administration section below
RESULTS	The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months 3 through 6. Efficacy analysis included the first 16 patients who received 6 months of treatment with Oxlumo and demonstrated positive results with a 71% (95% CI: 65, 77) reduction in spot urinary oxalate:creatinine ratio from baseline. Oxlumo demonstrated more positive results using secondary endpoints including additional measures of oxalate.
SAFETY	Safety profile observed was similar to that seen in ILLUMINATE-A

Contraindications [(4)]

- No documented contraindications

Warnings and Precautions [(4)]

- There are no available data with the use of Oxlumo in pregnant women, in human milk, the effects on the breastfed child, or the effects of the drug on milk production.

Adverse Effects [(4)]

Most common, ≥10%	Oxlumo N= (%)	Placebo N= (%)
Injection site reaction	26 (38)	0 (0)
Abdominal pain (upper, lower and discomfort included)	4 (15)	1 (8)

Drug Interactions [(4)]

- No clinical studies evaluating drug interaction potential of Oxlumo have been conducted.

Dosage and Administration [3,4]

Body Weight (actual)	Loading Dose	Maintenance Dose (begin 1 month after the last loading dose)
< 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to < 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
≥ 20 kg	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Year
Lumasiran	Oxlumo	Alnylam	210 mg every 3 months	$495,000

** Wholesale Acquisition Cost

Conclusion

Oxlumo is the first FDA-approved treatment for PH1. It works by interfering with mRNA in liver cells reducing the levels of GO enzyme, which reduces the amount of available glyoxylate, a substrate for oxalate production. The efficacy of Oxlumo was established in a double-blind study with 39 participants with PH1. Treatment with Oxlumo demonstrated a significant reduction in 24-hour urinary oxalate excretion corrected for BSA averaged over months 3 through 6. The most common adverse reactions are injection site reactions and abdominal pain.

Recommendation

The MO HealthNet Division recommends adding this drug to the Rare Disease Clinical Edit.

References

1) National Organization for Rare Disorders. Primary Hyperoxaluria. https://rarediseases.org/rare-diseases/primary-hyperoxaluria/. October 16, 2020.
2) Allena Pharmaceuticals. Hyperoxaluria. https://www.allenapharma.com/hyperoxaluria. Accessed November 27, 2020.
3) Medscape. Hypercalciuria Treatment & Management. https://emedicine.medscape.com/article/2182757-treatment#d9. Accesses November 27, 2020.
4) Oxlumo Package Insert. Cambridge, MA: Alnylam Pharmaceuticals; 2020. https://www.alnylam.com/wp-content/uploads/pdfs/OXLUMO-Prescribing-Information.pdf. Accessed November 25, 2020.
5) U.S. National Library of Medicine. Study of Lumasiran in Healthy Adults and Patient with Primary Hyperoxaluria Type 1. https://clinicaltrials.gov/ct2/show/results/NCT02706886?intr=%22ALN-GO1%22+OR+%22Lumasiran%22&draw=2&rank=5. October 14, 2020.
6) U.S. National Library of Medicine. A Study of Lumasiran in Infants and Young Children With Primary Hyperoxaluria Type 1. https://clinicaltrials.gov/ct2/show/NCT03905694?term=illuminate-b&draw=2&rank=1. Accessed November 25, 2020.

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