NEW DRUG APPROVAL

Brand Name	Oxlumo™
Generic Name	lumasiran
Drug Manufacturer	Alnylam Pharmaceuticals, Inc

New Drug Approval

FDA Approval Date: November 23, 2020

Review designation: Type 1 - New Molecular Entity Priority, Orphan

Type of Review: New Drug Application (NDA): 214103

Dispensing Restrictions: Speciality Only, Limited distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Primary hyperoxalurias (PHs) are caused by excess production of oxalate, a substance consumed in food and also produced by the body. PH1 is the most common and severe type. PH1 affects an estimated one to three individuals per million in North America and Europe and accounts for approximately 80% of PH cases.

Patients with PH1 produce far too much oxalate, which can combine with calcium to cause kidney stones and deposits in the kidneys. Patients can experience progressive kidney damage, which can lead to kidney failure and the need for dialysis (a treatment that purifies the blood). As kidney function worsens, oxalate can build up and damage other organs, including the heart, bones and eyes.

Primary Hyperoxalurias (PH) prevalence ranges from 1-3/1,000,000 and the estimated incidence is between 1-2/10,000,000 per year with no differences between sexes. There are higher rates reported in isolated populations, especially in the Middle East and North Africa. A significant proportion of patients are diagnosed at adulthood which implies an important under detection of patients. PH1 accounts for 85% of patients, PH2 8-10% and PH3 5-7%.

Efficacy

Oxlumo™ works to decrease oxalate production. It was evaluated in two studies in patients with PH1: a randomized, placebo-controlled trial in patients six years and older and an open-label study in patients younger than six years. Patients ranged in age from four months to 61 years at the first dose. In the first study, 26 patients received a monthly injection of Oxlumo™ followed by a maintenance dose every three months; 13 patients received placebo injections. The primary endpoint was the amount of oxalate measured in the urine over 24 hours. In the Oxlumo™ group, patients had, on average, a 65% reduction of oxalate in the urine, compared to an average 12% reduction in the placebo group. By the sixth month of the study, 52% of patients treated with Oxlumo™ reached a normal 24-hour urinary oxalate level; no patients treated with the placebo did.

In the second study, 16 patients younger than six years all received Oxlumo™. Using another measure of oxalate in the urine, the study showed, on average, a 71% decrease in urinary oxalate by the sixth month of the study.

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ILLUMINATE-A (NCT03681184) and ILLUMINATE-B (NCT03905694): Study Design Summary		
	ILLUMINATE-A	**ILLUMINATE-B**
Efficacy Results	• Treatment with Oxlumo resulted in a 65% mean reduction in urinary oxalate relative to baseline vs. 12% reduction reported in response to placebo, resulting in a mean treatment difference of 53% (95% CI: 45, 62; P <0.0001) • Oxlumo also achieved statistically significant results for six tested secondary endpoints • 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).	• Patients treated with Oxlumo achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 71% (95% CI: 65, 77). • The reduction of oxalate was consistent across all three body-weight categories. • Oxlumo also demonstrated positive results across secondary endpoints, including additional measures of oxalate.

Safety

ADVERSE EVENTS

The most common adverse reaction was injection site reaction (e.g. erythema, pain, pruritus, swelling), reported in ≥20% of patients. These symptoms were mild and resolved within 1 day of injection; they did not lead to discontinuation of Oxlumo™.

WARNINGS & PRECAUTIONS

Concerns related to adverse effects:

- Anti-lumasiran antibodies: Anti-drug antibodies were identified in 6% of patients during clinical trials, although no clinically significant differences in the safety, pharmacokinetic, or pharmacodynamic profiles were observed in patients who tested positive for anti-lumasiran antibodies.
- Injection site reactions: Injection site reactions, including erythema, pain, pruritus, and swelling, may occur; generally resolves within 1 day.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Lumasiran 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

lumasiran is independent of the underlying AGXT gene mutation. Oxlumo™ is not Reference ID: 4706370 expected to be 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.

Dose & Administration

ADULTS

3 mg/kg/dose subcutaneously once monthly for 3 doses, then 3 mg/kg/dose subcutaneously once every 3 months.

PEDIATRICS

Dosing is based on actual body weight.

Table 1. OXLUMO Weight-Based Dosing Regimen

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)

GERIATRICS

Clinical studies of Oxlumo™ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

RENAL IMPAIRMENT

No dose adjustment is necessary in patients with an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2 . Oxlumo™ has not been studied in patients with an eGFR <30 mL/min/1.73 m^2 or patients on dialysis.

HEPATIC IMPAIRMENT

No dose adjustment is recommended for patients with mild (total bilirubin > upper limit of normal (ULN) to 1.5 × ULN or AST > ULN) or moderate hepatic impairment (total bilirubin >1.5–3 × ULN with any AST). Oxlumo™ has not been studied in patients with severe hepatic impairment (total bilirubin >3 × ULN with any AST).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 94.5 mg/0.5 mL clear, colorless-to-yellow solution in a single-dose vial.