PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PROXLUMO®

Lumasiran Injection

Solution, 94.5 mg/0.5 mL lumasiran (as lumasiran sodium), subcutaneous injection

Various alimentary tract and metabolism products

Alnylam Netherlands B.V.

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RECENT MAJOR LABEL CHANGES

1. INDICATIONS	05/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OXLUMO (lumasiran) is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients.

1.1 Pediatrics

Pediatrics (< 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of OXLUMO in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dose Adjustment, 7.1.3 Pediatrics, 10.3 Pharmacokinetics, Special Populations and Conditions, and 14 CLINICAL TRIALS).

Limited data is available for patients <2 years of age and weighing <10 kilograms (kg). The efficacy of OXLUMO in PH1 patients <6 years of age was based on a single-arm trial (see 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (≥65 years): Clinical studies of OXLUMO did not include patients over the age of 65 (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

OXLUMO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- OXLUMO (lumasiran) is intended for subcutaneous use and should be administered by a health professional.
- It is supplied in a single-use vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.
- Once the vial is opened, use immediately.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosing regimen of OXLUMO consists of loading doses (once monthly for 3 doses) followed by maintenance doses (beginning 1 month after the last loading dose) as shown in Table 1 .

Dosing is based on body weight; therefore, regular weight monitoring is recommended.

Table 1 - OXLUMO Weight-Based Dosing Regimen

Body Weight	Loading Dose	Maintenance Dose (beginning 1 month after the last loading dose)
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly, beginning 1 month after the last loading dose.
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly): give the first maintenance dose 1 month after the last loading dose and quarterly thereafter.
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly): give the first maintenance dose 1 month after the last loading dose and quarterly thereafter.

The patient dose (in mg) and volume (in mL) should be calculated as follows:

Patient body weight (kg) × dose (mg/kg) = total amount (mg) of OXLUMO to be administered.

Total amount (mg) divided by concentration (189 mg/mL) = total volume of OXLUMO (mL) to be injected (see 4.4 Administration).

Use in Pediatrics

Dosing is based on body weight. No additional dose adjustments are required for pediatric patients. Limited data are available for patients <2 years of age and weighing <10 kg.

Use in Geriatrics

OXLUMO has not been studied in patients ≥65 years of age.

Renal Impairment

No dose adjustment is necessary in patients with renal impairment (eGFR <90 mL/min/1.73 m^2), including end-stage renal disease or those on hemodialysis (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Hepatic Impairment

No dose adjustment is necessary in patients with mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or aspartate aminotransferase [AST] > ULN) or moderate (total bilirubin >1.5 to 3 × ULN, any AST) hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions). Limited data are available in patients with mild or moderate hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions). OXLUMO has not been studied in patients with severe hepatic impairment.

4.3 Reconstitution

Reconstitution is not required.

4.4 Administration

OXLUMO is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-use vial, as a ready-to-use solution that does not require additional reconstitution or

dilution prior to administration. Inspect visually for particulate matter and discoloration. Do not use if discolored or if foreign particles are present.

Use aseptic technique.

- Calculate the required volume of OXLUMO based on the recommended weight-based dosage (see 4 DOSAGE AND ADMINISTRATION).
- Administer OXLUMO with a sterile 25- to 31-gauge needle with a 1/2- inch or 5/8-inch needle length for subcutaneous injection. For volumes less than 0.3 mL, a sterile 0.3 mL syringe is recommended.
- The maximum acceptable single injection volume is 1.5 mL. Doses requiring more than 1.5 mL should be administered as multiple injections to minimise potential injection site discomfort due to injection volume. Divide injection volumes greater than 1.5 mL equally into multiple syringes.
- Avoid having OXLUMO on the needle tip before the needle is in the subcutaneous space. Consider changing the needle prior to administration, if possible.
- Administer subcutaneous injection into the abdomen, thigh, or the side or back of the upper arms. Rotate injection sites. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.
    - If injecting into the abdomen, avoid the area around the navel.
    - If more than one injection is needed for a single dose of OXLUMO, the injection sites should be at least 2 cm apart.
    - Discard any unused portion of the drug.

Patients on Hemodialysis

Administer OXLUMO following hemodialysis if administered on dialysis days.

4.5 Missed Dose

If a dose is delayed or missed, administer OXLUMO as soon as possible. Resume prescribed monthly or quarterly dosing, from the most recently administered dose.

5 OVERDOSAGE

No cases of overdose with OXLUMO have been reported in clinical trials. In case of overdose, it is recommended that patients be monitored as medically indicated for any signs or symptoms of adverse effects and given appropriate treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Sterile solution 94.5 mg lumasiran per 0.5 mL (189 mg/mL)	Water for injection, sodium hydroxide, phosphoric acid

OXLUMO is a double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

OXLUMO is a sterile, preservative free, clear, colorless-to-yellow solution for subcutaneous injection. OXLUMO is supplied as a 0.5 mL solution in a single-use glass vial with a fluoropolymer-coated rubber stopper and an aluminum overseal with a flip-off button.

OXLUMO is available in cartons containing one single use vial.

7 WARNINGS AND PRECAUTIONS

Renal

OXLUMO causes a chronic stable increase in plasma glycolate levels (see 10.2 Pharmacokinetics). Patients with severe and/or end stage renal disease are at increased risk of metabolic acidosis. The risk of metabolic acidosis associated with exposure to prolonged higher levels of plasma glycolate in these patients is unknown. Caution should be taken, with monitoring for signs and symptoms of metabolic acidosis when OXLUMO is administered to this population.

Reproductive Health: Female and Male Potential

Fertility

There are no data on the effects of OXLUMO on human fertility. No adverse effects on male or female fertility were detected in animal studies (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on the use of OXLUMO in pregnant women.

The clinical need for OXLUMO during pregnancy should be considered along with expected health benefits to the mother and any potential adverse effects on the fetus from OXLUMO or from the underlying maternal condition.

Animal studies do not indicate direct harmful effects with respect to reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

There are no data on the presence of OXLUMO in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OXLUMO and any potential adverse effects on the breastfed infant from OXLUMO or from the underlying maternal condition.

7.1.3 Pediatrics

The safety and efficacy of OXLUMO have been established in pediatric patients (see 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY, and 14 CLINICAL TRIALS). Limited data is available for patients <2 years of age and weighing <10 kg.

7.1.4 Geriatrics

OXLUMO has not been studied in patients ≥65 years of age (see 10.3 Pharmacokinetics, Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data reflect placebo-controlled and open-label clinical studies in 98 patients with PH1 which includes 71 pediatric patients and 15 patients on hemodialysis. Patients ranged in age from 4 months to 61 years at first dose. Three patients were <1 year of age and 4 patients were between 1 to <2 years of age. The median duration of exposure was 18.99 months (range 2.8 to 34.7 months). Overall, 92 patients were treated for at least 6 months, and 78 patients for at least 12 months and 29 patients for at least 24 months.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Placebo-controlled study

In the randomized, placebo-controlled, double-blind study (ILLUMINATE-A) in pediatric and adult patients with PH1 aged 6 to 61 years, 26 patients received OXLUMO and 13 patients received placebo. Of these, 25 patients received ≥5 months of treatment. The most common (≥20%) adverse reaction reported was injection site reaction. All adverse reactions were non-serious, and none resulted in discontinuation of treatment.

Table 3 - Adverse Reactions Reported in at Least 10% of Patients Treated with OXLUMO and that Occurred at Least 5% More Frequently than in Patients Treated with Placebo in ILLUMINATE-A during the 6-Month Double-Blind Period

System Organ Class	Adverse reaction	OXLUMO N = 26 n (%)	Placebo N = 13 n (%)
Gastrointestinal disorders	Abdominal pain[a]	4 (15)	1 (8)
General disorders and administration site conditions	Injection site reaction	10 (38)	0 (0)

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort and abdominal tenderness

In two single-arm studies in patients with PH1, ILLUMINATE-B (patients <6 years of age) and ILLUMINATE-C (pediatric and adult patients with severe renal impairment including end-stage renal disease and patients on hemodialysis), the OXLUMO safety profile was similar to that seen in ILLUMINATE-A.

Description of selected adverse reactions

Injection site reactions (ISRs)

In placebo-controlled and open-label clinical studies, injection site reactions were reported in 34 of 98 patients (35%) treated with OXLUMO, occurring in 8% of injections. The most commonly reported symptoms were erythema, swelling, pain, hematoma, pruritus, and discoloration. The majority of ISRs had an onset within 1 to 3 days of the injection (with onset ranging from same day of administration to 29 days after the most recent dose). ISRs have been mild, transient, and have not resulted in discontinuation of treatment.

Abdominal Pain

In placebo-controlled and open-label clinical studies, abdominal pain was reported in 16 of 98 patients (16%) treated with OXLUMO. The adverse reaction of abdominal pain included abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort and abdominal tenderness. Most of the adverse reactions of abdominal pain were mild in severity, transient and none led to the discontinuation of treatment.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

No clinical drug interaction studies have been performed. Concomitant use of pyridoxine (vitamin B6) did not influence the pharmacodynamics or pharmacokinetics of lumasiran.

Lumasiran is not metabolized by cytochrome P450 (CYP) enzymes, and its pharmacokinetics are not expected to be influenced by other medications.

In vitro studies indicate that lumasiran is not a substrate nor an inhibitor of cytochrome P450 (CYP) enzymes.

As a GalNac-siRNA, lumasiran is not expected to inhibit or induce CYP enzymes or modulate the activities of drug transporters.

9.2 Drug-Food Interactions

OXLUMO is administered as a subcutaneous injection, therefore interactions with food are not expected.

9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lumasiran is a double-stranded siRNA that reduces the levels of the enzyme glycolate oxidase (GO) 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. This results in reduction of urinary and plasma oxalate levels, the underlying cause of disease manifestations in patients with PH1. As the GO enzyme is upstream of the alanine:glyoxylate aminotransferase (AGT) enzyme, the deficiency of which causes PH1, the mechanism of action of lumasiran is independent of the underlying *AGXT* gene mutation encoding AGT. OXLUMO is not 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 PH2 and PH3.

10.2 Pharmacodynamics

The pharmacodynamic effects of OXLUMO have been evaluated in adult and pediatric patients with PH1 across a range of doses and dosing frequencies. Dose-dependent reductions in urinary and plasma oxalate levels were observed, resulting in the selection of the recommended body weight-based loading and maintenance dosing regimens. With the recommended dosing regimens, rapid onset of effect was observed within two weeks after the first dose and maximal reductions in urinary and plasma oxalate were observed by the end of the loading dose phase. The maximal reductions in urinary and plasma oxalate were sustained with the maintenance dosing regimen thereafter. Consistent with lumasiran mechanism of action, suppression of GO activity led to an increase in plasma glycolate levels, indicating target engagement. Plasma glycolate levels reached a plateau at the end of the loading dose phase.

Cardiac electrophysiology

Lumasiran had no effect on the QTc interval in healthy subjects and patients with PH1 who received OXLUMO up to 6 mg/kg (n=52). A dedicated thorough QT study has not been conducted with OXLUMO.

10.3 Pharmacokinetics

The pharmacokinetic (PK) properties of OXLUMO were characterized by measuring the plasma and urine concentrations of lumasiran. Lumasiran exhibited approximately linear, time independent pharmacokinetics in plasma following single subcutaneous doses ranging from 0.3 to 6 mg/kg and multiple doses of 1 and 3 mg/kg once monthly or 3 mg/kg and 6 mg/kg quarterly. There was no accumulation of lumasiran in plasma after repeated once monthly or quarterly dosing.

Table 4 - Summary of Lumasiran Pharmacokinetic Parameters Across Studies

Weight group	Dose	Number of patients	C_{max} (ng/mL) Median (min, max)	$AUC_{0\text{-last}}$ (h*ng/mL) Median (min, max)	T_{max} (h) Median (min, max)	$T_{1/2}$ (h) Median (min, max)	CL (L/h) Median (min, max)
<10 kg	6 mg/kg	3	890 (678,1280)	6270 (5920,8510)	4.2 (2.0,8.1)	5.5[a]	5.6[a]
≥10 kg to <20 kg	6 mg/kg	11	912 (523,1760)	8110 (7050,13300)	3.7 (1.9,7.8)	4.5 (2.6,10.3)[b]	9.1 (6.25,10.2)[b]
≥20 kg	3 mg/kg	18	518 (205,2280)	6810 (2890,10700)	4.0 (0.5,12.0)	4.9 (1.4,10.9)[b]	18.0 (9.89,27.3)[b]

[a] n=1
[b] n=9

Absorption: Following subcutaneous administration, lumasiran is rapidly absorbed with a median (range) time to reach maximum plasma concentration (t_{max}) of 4.0 (0.5 to 12.0) hours.

Distribution: The protein binding of lumasiran is moderate to high (77 to 85%) at clinically relevant concentrations. The volume of distribution of lumasiran in humans was extrapolated from intravenous preclinical data. In PK modeling, it was estimated to be 4.9 L in a typical 70 kg adult patient.

Lumasiran primarily distributes from plasma to the liver after subcutaneous dosing.

Metabolism: Lumasiran is metabolized by endo- and exonucleases to oligonucleotides of shorter lengths. In vitro studies indicate that lumasiran does not undergo metabolism by CYP450 enzymes.

Elimination: Lumasiran is primarily eliminated from plasma by hepatic uptake, with only 7 to 26% of the administered dose recovered in urine as lumasiran. The mean (%CV) terminal plasma half-life of lumasiran is 5.2 (47.0%) hours. The population estimate for apparent

plasma clearance was 26.5 L/h for a typical 70 kg adult. The renal clearance of lumasiran was minor and ranged from 2.0 to 3.4 L/h.

Plasma concentrations do not reflect the extent or duration of the pharmacodynamic activity of lumasiran. Rapid and targeted uptake of lumasiran by the liver results in a rapid decline in plasma concentrations. In the liver, lumasiran exhibits a long half-life leading to maintenance of pharmacodynamic effect over the monthly or quarterly dosing interval.

Special Populations and Conditions

- ***Pediatrics:*** Data in children younger than 2 years of age and weighing <10 kg are limited. In children <20 kg, lumasiran C_{max} was 2-fold higher due to the nominally higher dose of 6 mg/kg and faster absorption rate. The pharmacodynamics of lumasiran were similar in pediatric patients (aged 4 months to 17 years) and in adults, despite the transiently higher plasma concentrations in children <20 kg, due to the rapid and predominant distribution of lumasiran to the liver.
- ***Geriatrics:*** OXLUMO has not been studied in patients aged ≥65 years.
- ***Sex:*** In clinical studies, there was no difference in the plasma exposure or pharmacodynamics of lumasiran based on sex.
- ***Hepatic Insufficiency:*** Limited data in patients with mild hepatic impairment (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or aspartate aminotransferase [AST] > ULN) or moderate hepatic impairment (total bilirubin >1.5 to 3 × ULN with any AST) showed comparable plasma exposure of lumasiran and similar pharmacodynamics as patients with normal hepatic function. OXLUMO has not been studied in patients with severe hepatic impairment.
- ***Renal Insufficiency:*** Patients with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment had comparable plasma exposure of lumasiran as patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2). In patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), end-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2), and patients on hemodialysis, within the same body weight category, a 1.8 to 3.6 fold higher C_{max} and 1.6 to 3.1 fold higher $AUC_{0\text{-last}}$ was observed. These increases were transient and not considered clinically relevant as the plasma concentrations declined to below the level of detection within 24 to 48 hours, similar to patients without renal impairment. The pharmacodynamics in patients with renal impairment (eGFR <90 mL/min/1.73 m^2), including ESRD (eGFR <15 mL/min/1.73 m^2) or those on dialysis were similar to patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2).
- ***Body weight:*** The recommended dosing regimens yielded up to 2-fold higher C_{max} in children <20 kg while $AUC_{0\text{-}24}$ was similar across the body weights studied (6.2 to 110 kg).

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

Store at 2°C to 30°C.

Keep OXLUMO vial in the original carton to protect from light until ready for use.

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

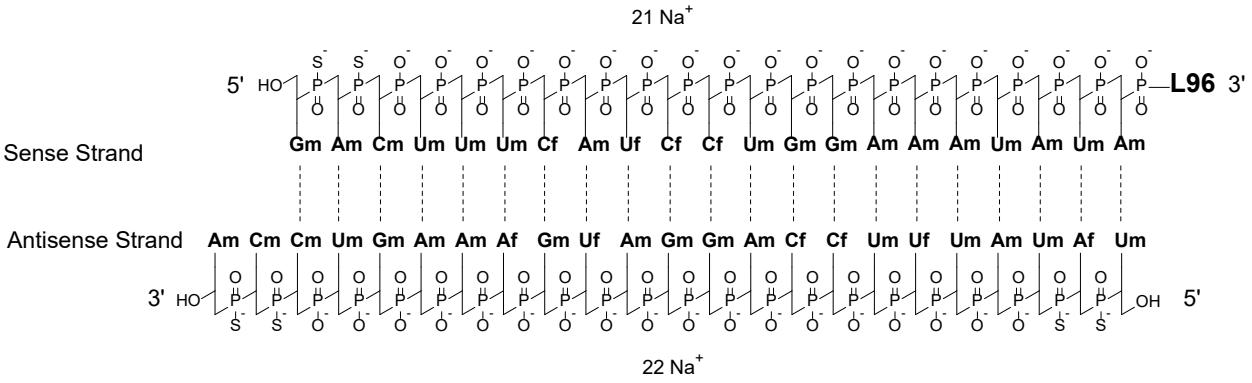
Drug Substance

Proper/Common name: lumasiran sodium

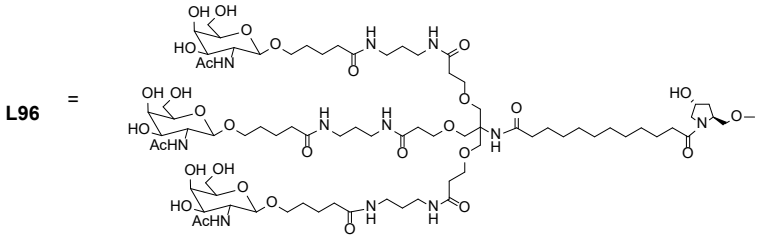
Molecular formula and molecular mass of lumasiran: The molecular formula of lumasiran is $C_{530}H_{712}F_{10}N_{173}O_{320}P_{43}S_6$ and the molecular mass is 16,340.54 Da.

Molecular formula and molecular mass of lumasiran sodium: The molecular formula of lumasiran sodium is $C_{530}H_{669}F_{10}N_{173}O_{320}P_{43}S_6Na_{43}$ and the molecular mass is 17,285.76 Da.

Structural formula:



(Af= adenine, Cf= cytosine, Uf= uracil)= 2'F ribonucleosides
(Am= adenine, Cm= cytosine, Gm= guanine, Um= uracil)= 2'OMe ribonucleosides
O⁻ = phosphodiester
S⁻ = Phosphorothioate
Dashed lines denote Watson-Crick base pairing



L96= Triantennary GalNAc (*N*-acetyl galactosamine)

Physicochemical properties:

- The lumasiran sodium drug substance is a white to pale yellow powder
- The solubility of lumasiran sodium drug substance in water has been determined to be at least 387 mg/mL
- pH of a 1% solution in 50 mM KCl: 5.0 to 8.0

14 CLINICAL TRIALS

14.1 Clinical Trials by Indications

Primary Hyperoxaluria Type 1

Trial Design and Study Demographics

Table 5 - Summary of Patient Demographics for Clinical Trials in PH1

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
ILLUMINATE-A	Phase 3, with two periods: • 6-month, randomized (2:1), placebo-controlled, DB period (primary analysis period) • Extension Period (up to 54 months)	• DB Period: Placebo or lumasiran 3 mg/kg qMx3; then, 3 mg/kg q3M* • Extension Period: Placebo patients crossed over to receive lumasiran 3 mg/kg qMx3; then, 3 mg/kg q3M* • Lumasiran patients continued to receive lumasiran 3 mg/kg q3M	lumasiran: 26 placebo: 13	14.9 (6 to 61) years	Male (66.7%) Female (33.3%)
ILLUMINATE-B	Phase 3, with two periods: • 6-month, single-arm, Primary Analysis Period • Extension Period (up to 54 months)	Lumasiran at: • <10 kg: 6 mg/kg qM×3; then, 3 mg/kg qM • 10 to <20 kg: 6 mg/kg qM×3; then, 6 mg/kg q3M • ≥20 kg: 3 mg/kg qM×3; then, 3 mg/kg q3M	lumasiran: 18	51.4 (4 to 74) months	Male (44.4%) Female (55.6%)

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
ILLUMINATE-C	Phase 3, with two periods: • 6-month, single-arm, Primary Analysis Period • Extension Period (up to 54 months)	Lumasiran at: • <10 kg: 6 mg/kg qM×3; then, 3 mg/kg qM • 10 to <20 kg: 6 mg/kg qM×3; then, 6 mg/kg q3M • ≥20 kg: 3 mg/kg qM×3; then, 3 mg/kg q3M	lumasiran: 21	8.0 (0 to 59) years	Male (57.1%) Female (42.9%)

DB = double-blind; q3M = once every 3 months; qM = once monthly; qMx3 = once monthly for 3 consecutive months (i.e. Day 1, Month 1, Month 2).
* Patients received loading doses of study drug qM for 3 doses (at Day 1, Month 1, and Month 2) followed by the first maintenance dose at Month 3 and then q3M.

The efficacy of OXLUMO was demonstrated in a randomized, double-blind, placebo-controlled clinical study in patients 6 years and older with PH1 (ILLUMINATE-A), in a single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B), and in a single-arm clinical study in pediatric and adult patients with PH1 who have advanced renal disease including patients on hemodialysis (ILLUMINATE-C).

ILLUMINATE-A

A total of 39 patients with PH1 were randomized 2:1 to receive subcutaneous doses of OXLUMO or placebo during the 6-month double-blind, placebo-controlled period. Patients 6 years and older with an eGFR ≥30 mL/min/1.73 m^2 were enrolled and received 3 loading doses of 3 mg/kg OXLUMO or placebo administered once monthly, followed by quarterly maintenance doses of 3 mg/kg OXLUMO or placebo (see 4 DOSAGE AND ADMINISTRATION) After the 6-month double-blind treatment period, patients, including those originally assigned to placebo, entered an extension period with administration of OXLUMO.

During the 6-month double-blind, placebo-controlled period, 26 patients received OXLUMO, and 13 received placebo. The median age of patients at first dose was 14.9 years (range 6.1 to 61.0 years), 66.7% were male, and 76.9% were White. The median 24-hour urinary oxalate excretion corrected for body surface area (BSA) at baseline was 1.72 mmol/24 hr/1.73 m^2, the median spot urinary oxalate:creatinine ratio at baseline was 0.21 mmol/mmol, and the median plasma oxalate level at baseline was 13.1 µmol/L. Overall, 33.3% of patients had normal renal function (eGFR ≥90 mL/min/1.73 m^2), 48.7% had mild renal impairment (eGFR of 60 to <90 mL/min/1.73 m^2), and 18% had moderate renal impairment (eGFR of 30 to <60 mL/min/1.73 m^2). The OXLUMO and placebo arms were balanced at baseline with respect to age, urinary oxalate level, and eGFR.

The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over Months 3 through 6.

ILLUMINATE-B

A total of 18 patients were enrolled and treated with OXLUMO in a multicenter, single-arm study in patients with PH1 (ILLUMINATE-B). The study enrolled patients less than 6 years of age with an eGFR >45 mL/min/1.73 m^2 in patients 12 months of age and older, and normal serum creatinine in patients less than 12 months of age.

At first dose, 3 patients were less than 10 kg, 12 were 10 kg to less than 20 kg, and 3 were 20 kg or above. Patients <10 kg received 6 mg/kg once monthly for 3 months, followed by monthly maintenance doses of 3 mg/kg of OXLUMO, patients 10 to <20 kg received 6 mg/kg once monthly for 3 months, followed by quarterly maintenance doses of 6 mg/kg of OXLUMO, and patients ≥20 kg received 3 mg/kg once monthly for 3 months, followed by quarterly maintenance doses of 3 mg/kg of OXLUMO. The median age of patients at first dose was 51.4 months (range 4 to 74 months), 55.6% were female, and 88.9% were White. The median spot urinary oxalate:creatinine ratio at baseline was 0.47 mmol/mmol.

The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio (averaged over Months 3 through 6).

ILLUMINATE-C

A total of 21 patients were enrolled and treated with OXLUMO in an on-going multi-center, single-arm study in patients with PH1 and advanced renal disease (eGFR ≤45 mL/min/1.73m^2 in patients 12 months of age and older and elevated serum creatinine in patients less than 12 months of age), including patients on hemodialysis. ILLUMINATE-C includes 2 cohorts: Cohort A consists of 6 patients who did not require hemodialysis at the time of study enrollment and Cohort B consists of 15 patients who were on a stable regimen of hemodialysis. Patients received the recommended dosing regimen of OXLUMO based on body weight (see 4. DOSAGE AND ADMINISTRATION).

The median age of patients at first dose was 8.9 years (range 0 to 59 years), 57.1% were male, and 76.2% were White. For Cohort A patients, the median plasma oxalate level was 57.94 µmol/L. For Cohort B patients, the median plasma oxalate level was 103.65 µmol/L at baseline.

Study Results

Table 6 - Results of studies ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C in PH1

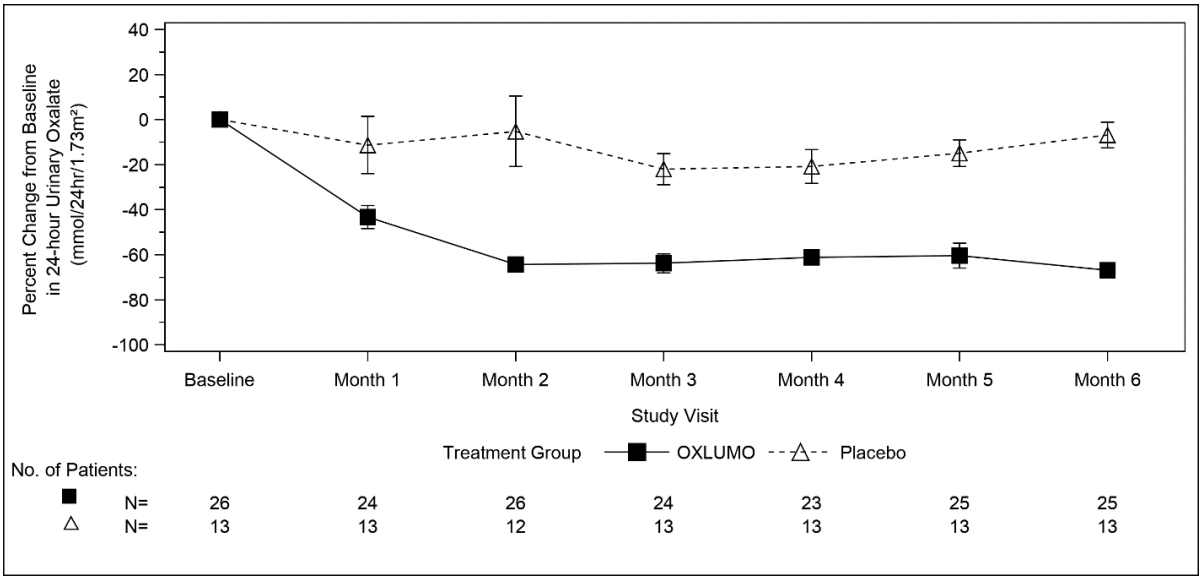
Study	Primary Endpoints	OXLUMO LS* mean % reduction (95% CI)	Placebo LS mean % reduction (95% CI)	Between-group LS mean % difference (95% CI)
ILLUMINATE-A	Percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA (averaged over Months 3 through 6)	65.4% (59.5, 71.3)	11.8% (4.1, 19.5)	53.5% (44.8, 62.3) p<0.0001
ILLUMINATE-B	Percent reduction from baseline in spot urinary oxalate:creatinine ratio (averaged over Months 3 through 6)	72.0% (66.4, 77.5)	NA	NA
ILLUMINATE-C	Percent reduction from baseline in plasma oxalate to Month 6 (averaged over Months 3 through 6)	Cohort A: 33.3% (-15.2, 81.8) Cohort B: 42.4% (34.2, 50.7)	NA	NA

NA = not applicable
* LS = least square

ILLUMINATE-A

OXLUMO was associated with a clinically meaningful least square (LS) mean percent reduction from baseline in 24-hour urinary oxalate of 65.4% (95% CI: 59.5, 71.3), compared with 11.8% (95% CI: 4.1, 19.5) in the placebo group, resulting in a statistically significant between-group LS mean difference of 53.5% (95% CI: 44.8, 62.3; p<0.0001). The reductions in urinary oxalate observed in patients treated with OXLUMO were rapid and sustained, as shown in Figure 1.

Figure 1 - ILLUMINATE-A: Percent Change from Baseline in 24-hour Urinary Oxalate Corrected for BSA by Month 6



Abbreviations: BL = baseline; BSA = body surface area; M = month; SEM = standard error of mean.
Results are plotted as mean (±SEM) of percent change from baseline.

At Month 6, a higher proportion of patients treated with OXLUMO achieved normal or near-normal levels of 24-hour urinary oxalate corrected for BSA (≤1.5×ULN) compared to placebo-treated patients, as shown in Table 7. Plasma oxalate levels were reduced during the 6-month double-blind period in patients treated with OXLUMO.

Table 7 - ILLUMINATE-A: Secondary Endpoint Results Over the 6-Month Double-Blind, Placebo-Controlled Period

Endpoints	OXLUMO (N=26)	Placebo (N=13)	Treatment Difference (95% CI)	P-value
Proportion of patients with 24-hour urinary oxalate levels at or below ULN‡	0.52 (0.31, 0.72)§	0 (0, 0.25)§	0.52 (0.23, 0.70)¶	0.001#
Proportion of patients with 24-hour urinary oxalate levels at or below 1.5×ULN‡	0.84 (0.64, 0.95)§	0 (0, 0.25)§	0.84 (0.55, 0.94)¶	<0.0001#

Abbreviations: ULN = upper limit of normal; SEM = standard error of mean.
Results are based on liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.
‡ ULN=0.514 mmol/24 hr/1.73 m^2 for 24-hour urinary oxalate corrected for BSA.
§ 95% CI based on Clopper Pearson Exact confidence interval.
¶ Calculated using the Newcombe Method based on the Wilson Score.
# p-value is based on Cochran-Mantel-Haenszel test stratified by baseline 24-hour urinary oxalate corrected for BSA (≤1.70 vs >1.70 mmol/24 hr/1.73 m^2).

In the Extension Period, 87.5% (21/24) of patients in the lumasiran/lumasiran group achieved near normalization (<1.5xULN) and 37.5% (9/24) of patients achieved normalization (<ULN) of 24-hour urinary oxalate levels at Month 12.

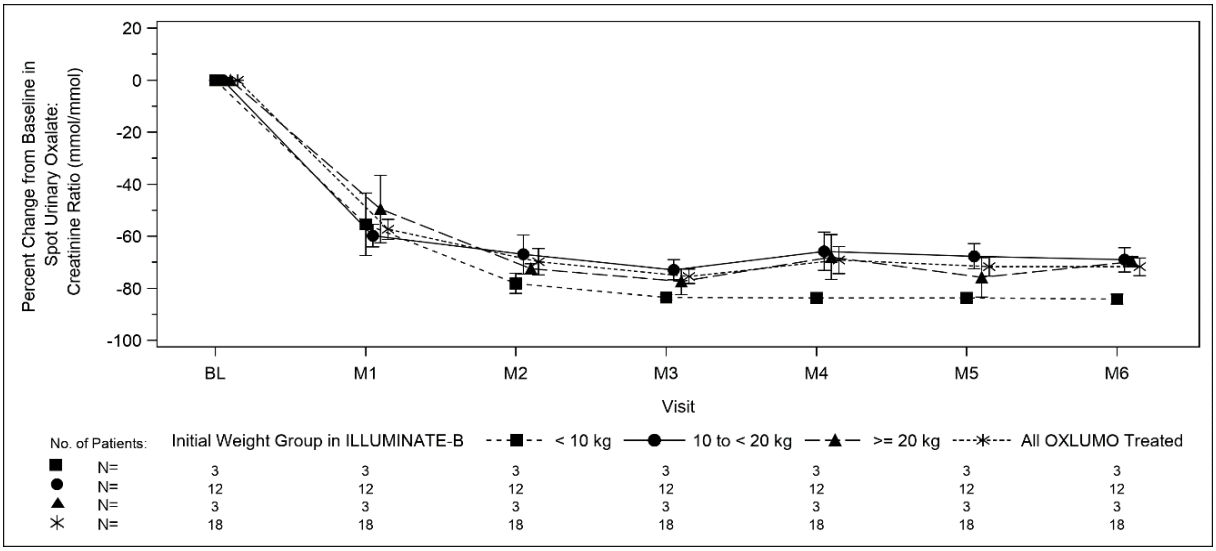
Reduced oxalate levels observed in the double-blind period were maintained with continued lumasiran treatment through Month 24. eGFR was assessed through the 6-month double-blind and extension periods for a total of 24 months and remained stable in patients administered OXLUMO.

ILLUMINATE-B

In the 6-month primary analysis, patients treated with OXLUMO achieved a LS mean percent reduction of 72.0% (95% CI: 66.4, 77.5) in spot urinary oxalate:creatinine ratio from baseline (averaged over Months 3 through 6), the primary endpoint. OXLUMO was associated with rapid, and sustained reductions in spot urinary oxalate:creatinine ratio (Figure 2), which were similar across all weight strata.

The percent reduction in urinary oxalate excretion was maintained with continued lumasiran treatment through month 12 and consistent with data from ILLUMINATE-A.

Figure 2 - ILLUMINATE-B: Percent Change from Baseline in Spot Urinary Oxalate:Creatinine Ratio by Month 6



Abbreviations: BL = baseline; M = month; SEM = standard error of mean.
Results are plotted as mean (±SEM) of percent change from baseline.

At Month 6, nine of 18 patients achieved near normalization (≤1.5×ULN), including 1 patient who achieved normalization (≤ULN), in spot urinary oxalate:creatinine ratio

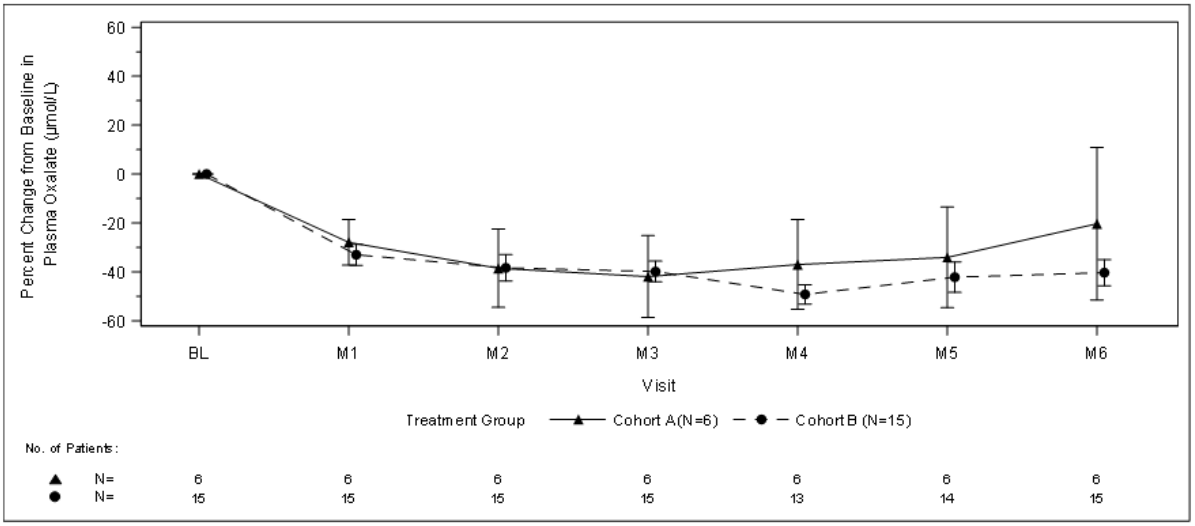
From baseline to Month 6 (average from Month 3 to Month 6), an LS mean plasma oxalate reduction of 31.7% (95% CI: 23.9, 39.5) was observed. During the 6-month period eGFR remained stable.

ILLUMINATE-C

The primary endpoint of the study was the percent change in plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort A (N=6) and the percent change in pre-dialysis plasma oxalate from baseline to Month 6 (average from Month 3 to Month 6) for Cohort B (N=15).

During the 6-month primary analysis period, patients in both cohorts had a reduction in plasma oxalate as early as Month 1. The percent reduction from baseline to Month 6 (average from Month 3 to Month 6) in plasma oxalate levels for Cohort A was an LS mean difference of 33.3% (95% CI: -15.2, 81.8) and for Cohort B the LS mean difference was 42.4% (95% CI: 34.2, 50.7).

Figure 3 - ILLUMINATE-C: Percent Change from Baseline in Plasma Oxalate at Each Visit during the Primary Analysis Period



Abbreviations: BL = baseline; M = month; SEM = standard error of mean.
Results are plotted as mean (±SEM) of percent change from baseline.
For Cohort A, the baseline is defined as the mean of all plasma oxalate samples collected prior to the first dose of lumasiran; for Cohort B, the baseline is defined as the last four pre-dialysis plasma oxalate samples collected prior to the first dose of lumasiran. In Cohort B, only pre-dialysis samples are utilized.

In Cohort A the mean (SD) eGFR was 19.85 (9.6) mL/min/1.73m^2 at baseline and 16.43 (9.8) mL/min/1.73m^2 at Month 6.

14.3 Immunogenicity

Across all clinical studies in the OXLUMO development program, including patients with PH1 and healthy volunteers dosed with OXLUMO, 7 of 120 (6%) of lumasiran-treated individuals tested positive for antidrug antibodies (ADA). ADA titers were low and generally transient.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described above with the incidence of antibodies in other studies or to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In repeat-dose toxicity studies, microscopic changes (e.g. hepatocellular vacuolation and karyomegaly) and decreased fibrinogen levels were observed mainly in rats at doses ≥20 mg/kg, and cholesterol levels were mildly increased at doses ≥50 mg/kg. A mild increase in alkaline phosphatase activity was observed in male rats (at 200 mg/kg) and in male monkeys (doses ≥30 mg/kg).

Carcinogenicity: Lumasiran was not carcinogenic in Sprague Dawley rats following monthly subcutaneous administration for at least 94 weeks (males), and at least 88 weeks (females) at doses of 20, 55, or 110 mg/kg (3, 9, or 18 times the normalized maintenance MRHD, based on body surface area).

Lumasiran was not carcinogenic in transgenic Tg-rasH2 mice following monthly subcutaneous administration for 26 weeks at doses of 150, 500 or 1500 mg/kg.

Genotoxicity: Lumasiran was not genotoxic. Lumasiran was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay up to 5000 µg/plate in five bacteria strains. Lumasiran was not clastogenic in an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes at concentrations up to 500 µg/mL, nor in an in vivo micronucleus assay in rat bone marrow at doses up to 2000 mg/kg.

Reproductive and Developmental Toxicology: In embryo-fetal development studies in pregnant rats and pregnant rabbits, lumasiran was administered once daily by subcutaneous injection at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 6 through 17 for rats and 7 through 19 for rabbits). In both species, minimal decreases in maternal food consumption and maternal absolute body weights were observed at ≥3 mg/kg/day. Lumasiran was not detected in any fetus of either species and no effects on embryo-fetal survival or fetal body weights were observed. However, in rat fetuses, skeletal abnormalities (e.g. bipartite ossification of sternebrae and misshapen cervical arches) were observed at 30 mg/kg. In rabbit fetuses, visceral and skeletal abnormalities (e.g. detached ribs, fused mandibles) were observed at low doses 3 mg/kg and 10 mg/kg. The mechanisms behind the observed abnormalities remain unknown in both species.

In a peri- and postnatal development study, lumasiran administered subcutaneously to pregnant female rats on gestational days 7, 13, 19 and on lactation days 6, 12, and 18 through weaning at doses up to 50 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

Special Toxicology: Lumasiran is not considered to have an immunostimulatory or immunotoxicity potential, based on an absence of findings in nonclinical studies. Of note, OXLUMO was detected in semen of rabbits at 3 mg/kg and 30 mg/kg. Increased atypical residual bodies (basophilic and globular bodies) were observed in the seminiferous tubules of male Tg-rasH2 mice at doses ≥500 mg/kg, however, no degenerative or atrophic changes were noted.

Juvenile Toxicity: In juvenile rats, *HAO1* mRNA silencing of approximately 90% was observed on postnatal Day 33 relative to baseline, at doses ≥10 mg/kg. A minimal to mild fibrinogen concentration decrease (-13% to -40% from mean of control) in both sexes at doses ≥10 mg/kg and a minimal to moderate glucose concentration increase at doses ≥30 mg/ kg were observed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PROXLUMO®

Lumasiran Injection

Read this carefully before you start taking **OXLUMO** and before each dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your health professional about your medical condition and treatment and ask if there is any new information about **OXLUMO**.

What is OXLUMO used for?

OXLUMO is used to lower oxalate levels in the urine and blood in adults and children with primary hyperoxaluria type 1 (PH1).

How does OXLUMO work?

PH1 is an illness where the liver makes too much of a substance called oxalate. Oxalate is removed by the kidneys and is passed out in urine.

Lumasiran, the active substance in OXLUMO, reduces the amount of an enzyme called glycolate oxidase that the liver makes. Glycolate oxidase is one of the enzymes involved in producing oxalate. By lowering the amount of the enzyme, the liver produces less oxalate and the levels of oxalate in the urine and blood also fall. This can help to reduce the effects of PH1.

What are the ingredients in OXLUMO?

Medicinal ingredients: lumasiran (as lumasiran sodium)

Non-medicinal ingredients: phosphoric acid, sodium hydroxide, and water for injection

OXLUMO comes in the following dosage forms:

Solution for injection: 94.5 mg / 0.5 mL

Do not use OXLUMO if:

- You are allergic to lumasiran, or any of the other ingredients of this medicine. If you are not sure, talk to your healthcare professional before you are given this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OXLUMO. Talk about any health conditions or problems you may have, including if you:

- have severe kidney problems. Your healthcare professional may monitor you for signs of a build-up of acid in your body (metabolic acidosis).
- are on hemodialysis treatment.
- are pregnant or planning on becoming pregnant. It is not known if OXLUMO will harm your unborn child.
- are breast-feeding or planning to breastfeed. You and your healthcare professional should decide if the benefit of breastfeeding is greater than the risk to your baby. This is because this medicine may pass into the breast milk and it is not known how it will affect the baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with OXLUMO:

Interactions with other drugs are not known at this time.

How to take OXLUMO:

- OXLUMO will be given to you by a healthcare professional.
- It is given as an injection under the skin. This is called subcutaneous injection. It will be given in your stomach area (abdomen), thigh, or the side or back on your upper arm. The site of injection will rotate.
- You will receive your first doses (loading doses) once a month for 3 months. Your maintenance dosing will start 1 month after the last loading dose.

Usual dose:

Your healthcare professional will determine how much OXLUMO to give you. Your dose will depend on your body weight. Your healthcare professional will adjust your dose as your weight changes.

You will be given your first doses (loading dose) once a month for 3 doses. You will then start maintenance dosing one month after your last loading dose.

Body Weight	Loading dose First 3 months (for 3 doses)	Maintenance Dose Beginning 1 month after last loading dose (4th dose and onwards)
Less than 10 kg	6 mg for every kg you weigh, once a month	3 mg for every kg you weigh, once a month
10 kg to less than 20 kg	6 mg for every kg you weigh, once a month	6 mg for every kg you weigh, once every 3 months
20 kg or more	3 mg for every kg you weigh, once a month	3 mg for every kg you weigh, once every 3 months

Overdose:

If you think you, or a person you are caring for, have taken too much OXLUMO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed an appointment for your injection, talk to your healthcare professional as soon as possible.

What are possible side effects from using OXLUMO?

These are not all the possible side effects you may have when taking OXLUMO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Redness, pain, itching, or swelling at the site of the injection
- Stomach pain or discomfort

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 2°C to 30°C.
- Keep OXLUMO vial in the original carton to protect from light until ready for use.
- Keep out of reach and sight of children.
- Do not use this medicine after the expiration date, which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

If you want more information about OXLUMO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (https://www.alnylam.ca/), or by calling 1-877-256-9526.

This leaflet was prepared by Alnylam Netherlands B.V.

Last Revised: DEC 01, 2023