OXLUMO® (lumasiran) is the

FIRST APPROVED TREATMENT FOR PRIMARY HYPEROXALURIA TYPE 1 (PH1)

What is OXLUMO® (lumasiran)?

OXLUMO is a prescription medicine for the treatment of primary hyperoxaluria type 1 (PH1) to lower oxalate in urine and blood in children and adults.

IMPORTANT SAFETY INFORMATION

The most common side effect of OXLUMO is injection site reaction (redness, swelling, pain, bruising, itching, and discoloration at the site of injection). These are not all the possible side effects of OXLUMO. Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

*Alnylam is proud to feature real patients in our advertising. They may or may not be on an Alnylam therapy.

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

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Welcome

This brochure provides educational information for you and your loved ones about PH1 and can help you understand more about OXLUMO® (lumasiran).

Be sure to talk to your doctor about any questions you may have about treatment and PH1.

Natalie
Person with PH1

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

TABLE OF CONTENTS

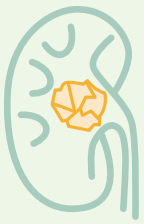
Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

Understanding PH1

PH1 is a rare genetic disease that can affect you or your loved ones. If you have PH1, it is important to work with your doctor.

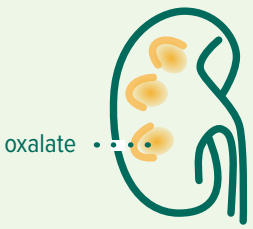
PH1 causes the body to produce too much oxalate, which can lead to kidney stones and kidney damage

KIDNEY



Kidney stones are the most common symptom of PH1

Any kidney stone in a child or adolescent, or recurring stones in adults, can be a sign of PH1.



PH1 is more than a kidney stone disease

Even if someone is not experiencing kidney stones, too much oxalate can cause serious damage to their kidneys or other organs.

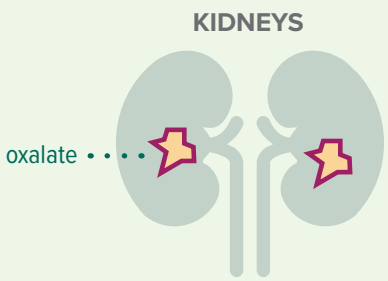
PH1 can cause kidney failure that may require hemodialysis and may necessitate kidney transplantation, or kidney and liver transplantation.

A liver transplant addresses the underlying genetic defect.

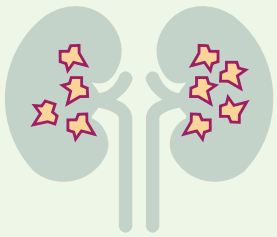
Why PH1 symptoms occur

Too much oxalate causes the symptoms of PH1

When you have too much oxalate in the body, this can lead to permanent damage of the kidneys and other areas of the body. PH1 may require ongoing management and monitoring with your doctor and a well-coordinated care team. This may include nephrologists, urologists, nurses, and other healthcare providers.



Oxalate is a waste product that is mostly removed by the kidneys through urine



When too much oxalate is made, it can damage the kidneys

When the disease advances and the kidneys aren't working right, oxalate can collect in the blood

Oxalate may then deposit in other organs and cause injury and permanent damage

Talk to your doctor about reducing oxalate production in PH1.

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

What is OXLUMO® (lumasiran)?

OXLUMO is the FIRST APPROVED treatment for primary hyperoxaluria type 1 (PH1) in infants, children, and adults.

Ask your doctor if OXLUMO fits into your management plan.

Grace
*Person with PH1**

IMPORTANT SAFETY INFORMATION

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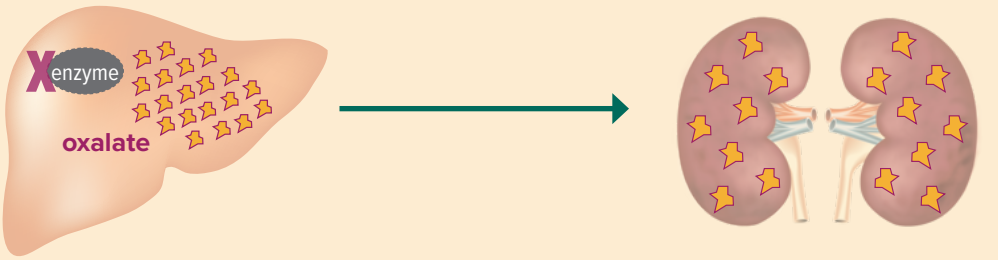
How OXLUMO® (lumasiran) works

Introduction to OXLUMO

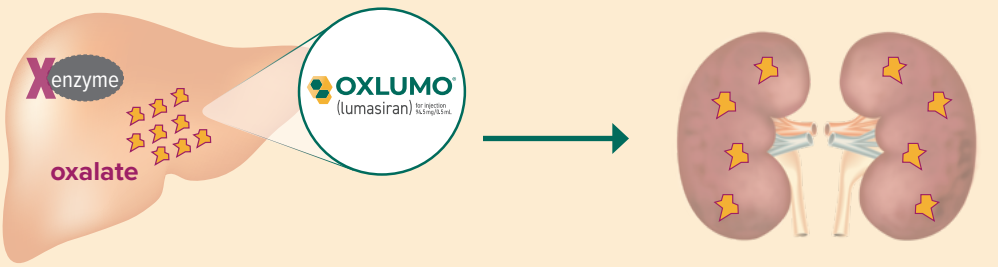
OXLUMO is designed to reduce the amount of oxalate produced by the body.

OXLUMO targets oxalate production at the source

In PH1, the liver continuously produces too much oxalate



OXLUMO works in the liver to reduce the amount of oxalate being made



IMPORTANT SAFETY INFORMATION

OXLUMO has not been studied in pregnant or breastfeeding women. Talk to your doctor about the risk of taking OXLUMO if you are pregnant, plan to become pregnant, are breastfeeding, or plan to breastfeed.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

How OXLUMO® (lumasiran) was tested in adults and children 6 years and older

In one of the clinical trials, OXLUMO was tested against placebo for 6 months in 39 adults and children 6 years and older who were diagnosed with PH1, did not have advanced kidney disease, and were not on hemodialysis:

- 26 received treatment with OXLUMO
- 13 received a placebo (an injection containing no medicine)

After 6 months, those initially on placebo were switched to OXLUMO, while patients who were receiving OXLUMO continued receiving OXLUMO.

Because urine is the main way oxalate is removed by the kidneys, the trial looked at the amount of oxalate in urine.

IMPORTANT SAFETY INFORMATION

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Natalie
Person with PH1

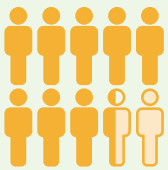
OXLUMO® (lumasiran) lowered urinary oxalate levels

53%

After 6 months of treatment, patients on OXLUMO had 53% less oxalate in their urine than patients on placebo

- **Patients initially on placebo who switched to OXLUMO had similar reductions in urinary oxalate after 6 months of treatment**
- **Patients initially on OXLUMO continued to have reduced urinary oxalate after 24 months of treatment**

Most patients treated with OXLUMO had normal or close-to-normal urinary oxalate levels*



84%

of patients treated with OXLUMO had normal (52%) or close-to-normal (32%) oxalate levels* in their urine after 6 months of treatment vs 0% of patients on placebo

*A normal level of oxalate in the urine means that oxalate levels were no longer elevated above the normal range. A close-to-normal level of oxalate in the urine means that oxalate levels were above the normal range, but were not more than 1.5 times above the normal range.

IMPORTANT SAFETY INFORMATION

OXLUMO has not been studied in pregnant or breastfeeding women. Talk to your doctor about the risk of taking OXLUMO if you are pregnant, plan to become pregnant, are breastfeeding, or plan to breastfeed.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

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How OXLUMO® (lumasiran) was tested in infants and children younger than 6 years

In another clinical trial, OXLUMO was studied in 18 patients (infants and children younger than 6 years old) diagnosed with PH1, who did not have advanced kidney disease, and were not on hemodialysis:

- All patients in the study received treatment with OXLUMO for the initial 6 months, then continued receiving OXLUMO

Because urine is the main way oxalate is removed by the kidneys, the trial looked at the amount of oxalate in urine.

OXLUMO reduced urinary oxalate levels* in younger patients

72%

Patients treated with OXLUMO had 72% less urinary oxalate* after 6 months of treatment compared to the start of the study continued to have less urinary oxalate through month 12

*Measured by the ratio of oxalate in the urine to creatinine level.

IMPORTANT SAFETY INFORMATION

The most common side effect of OXLUMO is injection site reaction (redness, swelling, pain, bruising, itching, and discoloration at the site of injection). These are not all the possible side effects of OXLUMO. Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

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OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

OXLUMO® (lumasiran) was also tested in patients with advanced disease, including people on hemodialysis

In an additional clinical trial, OXLUMO was studied in 21 patients of all ages (including infants younger than 1 year old) diagnosed with PH1 who had advanced kidney disease. The patients were divided into 2 groups:

- Group A was made up of 6 patients who were **not** on hemodialysis
- Group B was made up of 15 patients who were on hemodialysis

All patients in the study received treatment with OXLUMO for the initial 6 months, then continued receiving OXLUMO.

The trial looked at the amount of oxalate in blood, which is where it collects in patients who have advanced kidney disease.

OXLUMO reduced blood oxalate levels in patients with advanced disease, including those on hemodialysis

↓33%

Group A: Patients not on hemodialysis

GROUP A:
Patients treated with OXLUMO had 33% less blood oxalate after 6 months of treatment compared to the start of treatment

↓42%

Group B: Patients on hemodialysis

GROUP B:
Patients treated with OXLUMO had 42% less blood oxalate (measured before hemodialysis session) after 6 months compared to the start of treatment

IMPORTANT SAFETY INFORMATION

OXLUMO has not been studied in pregnant or breastfeeding women. Talk to your doctor about the risk of taking OXLUMO if you are pregnant, plan to become pregnant, are breastfeeding, or plan to breastfeed.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

Safety profile of OXLUMO® (lumasiran)

Clinical trials evaluated the safety profile of OXLUMO in 98 patients with PH1. Patients were 4 months to 61 years old at first dose. Ninety-two patients were treated for at least 6 months, 78 patients for at least 12 months, and 29 patients for at least 24 months.

The most common side effect in OXLUMO clinical trials was injection site reaction. Symptoms included redness, swelling, pain, bruising, itching, and discoloration at the site of the injection. Symptoms were generally mild, resolved within one day of injection, and did not result in stopping treatment.

The most common side effects in a 6-month clinical trial of 39 adults and children (age 6 and up) treated with OXLUMO were:

Injection site reaction

Abdominal pain

Symptoms included stomach pain or discomfort.

In two separate studies, one of infants and children younger than 6 years and another of patients with advanced kidney disease including patients on hemodialysis who all received OXLUMO, OXLUMO had a similar safety profile to the study above.

Each patient will respond differently to treatment with OXLUMO.
Talk to your doctor about any and all side effects you experience.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

Dosing for OXLUMO® (lumasiran)

OXLUMO is given by a healthcare provider as an injection under the skin in the abdomen, thighs, or upper arms. Dosing is based on the patient's weight.

Dosing for OXLUMO happens in 2 phases

STARTING DOSES

The first 4 doses are taken a month apart. The first 3 are starting doses to **help bring oxalate levels down**. The 4th is the first ongoing dose.

MONTHS

If a dose is delayed or missed, contact your doctor as soon as possible.

ONGOING DOSING

Ongoing dosing is quarterly (every 3 months) or monthly, **depending on the patient's weight**.

1ST ONGOING DOSE

For children under 10 kg (22 lb), 1 DOSE EVERY MONTH

For patients weighing 10 kg (22 lb) or more, 1 DOSE EVERY 3 MONTHS

- For patients on hemodialysis, OXLUMO will be administered after hemodialysis if administered on dialysis days

For more information about how OXLUMO is given, talk to your doctor.

IMPORTANT SAFETY INFORMATION

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OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Partner with the Alnylam Assist™ team

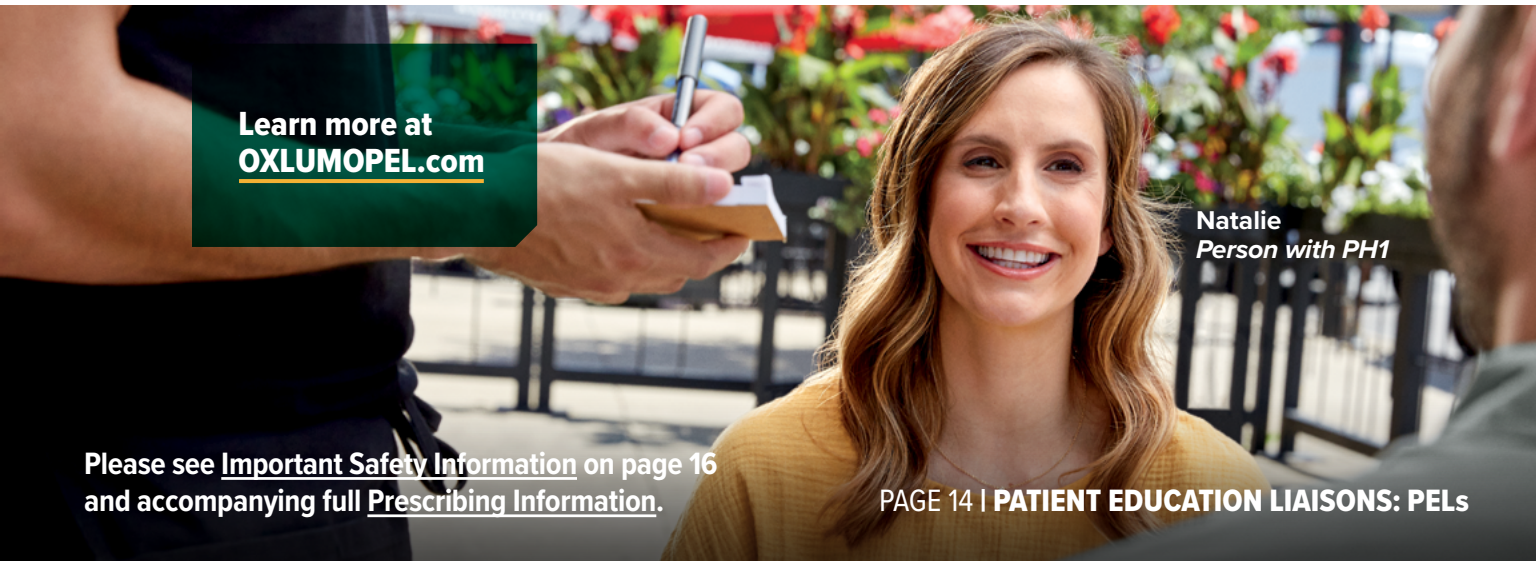
Once you and your doctor decide to begin treatment with OXLUMO® (lumasiran), and enroll in Alnylam Assist™, you will be paired with an Alnylam Case Manager in your area and have access to an Alnylam Patient Education Liaison.

Patient Education Liaisons (PELs) can help:

- **Support you with understanding PH1**
- **Help you understand how OXLUMO works**
- **Answer questions about treatment with OXLUMO**
- **Connect you with additional resources**

Learn from a PEL

- **PELs have backgrounds in nursing** and are experienced in educating patients and families about PH1 and providing information about treatment with OXLUMO
- **The purpose of the PEL program is to provide education** for patients, their families, and caregivers
- **PELs are employees of Alnylam Pharmaceuticals**. They are not acting as healthcare providers and are not part of your healthcare team
- **PELs do not provide medical care or advice**. All diagnosis and treatment decisions should be made by you and your doctor



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Alnylam Assist™ is here to help

Alnylam offers a support program for patients receiving OXLUMO® (lumasiran).

Support services include:

An Alnylam Case Manager

Case Managers are trained professionals whose expertise is in helping patients get started on treatment and providing product support.

Understanding Your Benefits

An Alnylam Case Manager will review your insurance coverage and answer questions about your insurance benefits for treatment with OXLUMO.

Financial assistance

Alnylam offers financial assistance programs for eligible patients. After being prescribed OXLUMO, you can talk to a Case Manager to learn if you may be eligible.*

Alnylam ASSIST®

To learn more about Alnylam Assist™ or to access materials:

Visit
AlnylamAssist.com

Call
1-833-256-2748
Monday-Friday,
8 AM-6 PM

Complete the Start Form

Get started on treatment with OXLUMO with a Start Form that you and your doctor can fill out.

Alnylam Assist™ is here to help you access therapy

*Individuals must meet specified criteria to qualify for assistance. Alnylam reserves the right to make determinations and to modify or discontinue the program at any time.

Please see Important Safety Information on page 16 and accompanying full Prescribing Information.

OXLUMO® (lumasiran) IS THE FIRST APPROVED PH1 TREATMENT FOR ALL AGES

OXLUMO works by reducing oxalate production in PH1

OXLUMO has been studied in infants, children, and adults with PH1

OXLUMO has been studied in patients who have advanced kidney disease, including patients receiving hemodialysis

Alnylam Assist™ is here to help you access therapy

Grace
*Person with PH1**

*Alnylam is proud to feature real patients in our advertising. They may or may not be on an Alnylam therapy.

Talk to your doctor to find out if OXLUMO is the right choice for you.

What is OXLUMO® (lumasiran)?

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OXLUMO has not been studied in pregnant or breastfeeding women. Talk to your doctor about the risk of taking OXLUMO if you are pregnant, plan to become pregnant, are breastfeeding, or plan to breastfeed.

For additional information about OXLUMO, please see accompanying full Prescribing Information.

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Alnylam® PHARMACEUTICALS

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXLUMO® safely and effectively. See full prescribing information for OXLUMO.

OXLUMO (lumasiran) injection, for subcutaneous use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2022
Dosage and Administration (2.1)	10/2022

---------- INDICATIONS AND USAGE----------

OXLUMO is a *HAO1*-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of OXLUMO by subcutaneous injection is based on body weight. (2.1)

Body Weight	Loading Dose	Maintenance 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), beginning 1 month after the last loading dose
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose

See Full Prescribing Information for important preparation and administration instructions. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 94.5 mg/0.5 mL in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

- None. (4)

---------- ADVERSE REACTIONS ----------

The most common adverse reaction (reported in ≥20% of patients) is injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OXLUMO is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients *[see Clinical Pharmacology (12.1), Clinical Studies (14.1, 14.2, 14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

Dosing is based on actual body weight.

Table 1. OXLUMO Weight-Based Dosing Regimen

Body Weight	Loading Dose	Maintenance 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), beginning 1 month after the last loading dose
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose

For Patients on Hemodialysis

Administer OXLUMO after hemodialysis if administered on dialysis days.

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.

2.2 Administration Instructions

OXLUMO is intended for subcutaneous use and should be administered by a healthcare professional.

Visually inspect the drug product solution. Do not use if it contains particulate matter or if it is cloudy or discolored. OXLUMO is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-dose vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.

- Use aseptic technique.

- Divide injection volumes greater than 1.5 mL equally into multiple syringes.
- For volumes less than 0.3 mL, a sterile 0.3-mL syringe is recommended. If using a 0.3 mL (30 unit) insulin syringe, 1-unit markings indicate 0.01 mL.
- 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 unused portion of the drug.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXLUMO has been evaluated in a placebo-controlled trial and two single-arm clinical trials. Across these trials, 98 patients with PH1 have been treated with OXLUMO, including 71 pediatric patients and 15 patients on hemodialysis. Overall, 92 patients were treated for at least 6 months, 78 patients for at least 12 months, and 29 patients for at least 24 months.

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.

In two single-arm studies in patients with PH1, ILLUMINATE-B (patients <6 years of age) and ILLUMINATE-C (pediatric and adult patients with moderately or severely reduced GFR [eGFR ≤45 mL/min/1.73 m^2 or pediatric patients <12 months of age with serum creatinine above the upper limit of normal for age] and patients with kidney failure on hemodialysis), the OXLUMO safety profile was similar to that seen in ILLUMINATE-A *[see Clinical Studies (14)]*.

In placebo-controlled and open-label clinical studies the most common adverse reaction reported was injection site reaction. Injection site reactions included erythema, swelling, pain, hematoma, pruritus, and discoloration. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment.

Table 2. 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

Adverse Reaction	OXLUMO N = 26 N (%)	Placebo N = 13 N (%)
Injection site reaction	10 (38)	0 (0)
Abdominal pain*	4 (15)	1 (8)
*Grouped term includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort		

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with the use of OXLUMO in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

No adverse effects on pregnancy or embryo-fetal development related to OXLUMO were observed in rats at 45 times and in rabbits at 90 times the maximum recommended human dose in women (see *Data*).

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 6-17). Administration of lumasiran resulted in no effects on embryo-fetal survival or fetal body weights and no lumasiran-related fetal malformations were observed. The 30 mg/kg/day dose in rats is 45 times the maximum recommended human dose (MRHD) for women of 3 mg/kg/month normalized to 0.1 mg/kg/day, based on body surface area. In an embryo-fetal development study in female rabbits, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 7-19). There were decreases in maternal food consumption and decreases in maternal body weight gains at doses $\geq$ 3 mg/kg/day. There were no lumasiran-related fetal findings identified at doses up to 30 mg/kg/day (90 times the normalized MRHD based on body surface area).

In a 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.

8.2 Lactation

Risk Summary

There are no data on the presence of OXLUMO in human milk, the effects on the breastfed child, or the effects of the drug 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 child from OXLUMO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of OXLUMO have been established in pediatric patients aged birth and older. Use of OXLUMO in these age groups is supported by evidence from an adequate and well controlled study of OXLUMO in pediatric patients 6 years or older and adults with PH1 (ILLUMINATE-A), a single-arm clinical study in pediatric patients less than 6 years of age with PH1 (ILLUMINATE-B), and a single-arm clinical study in pediatric and adult patients with PH1 who had advanced chronic kidney disease including patients on hemodialysis (ILLUMINATE-C) *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

8.5 Geriatric Use

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

8.6 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 to 3 × ULN with any AST). OXLUMO has not been studied in patients with severe hepatic impairment (total bilirubin > 3 × ULN with any AST) *[see Clinical Pharmacology (12.3)]*.

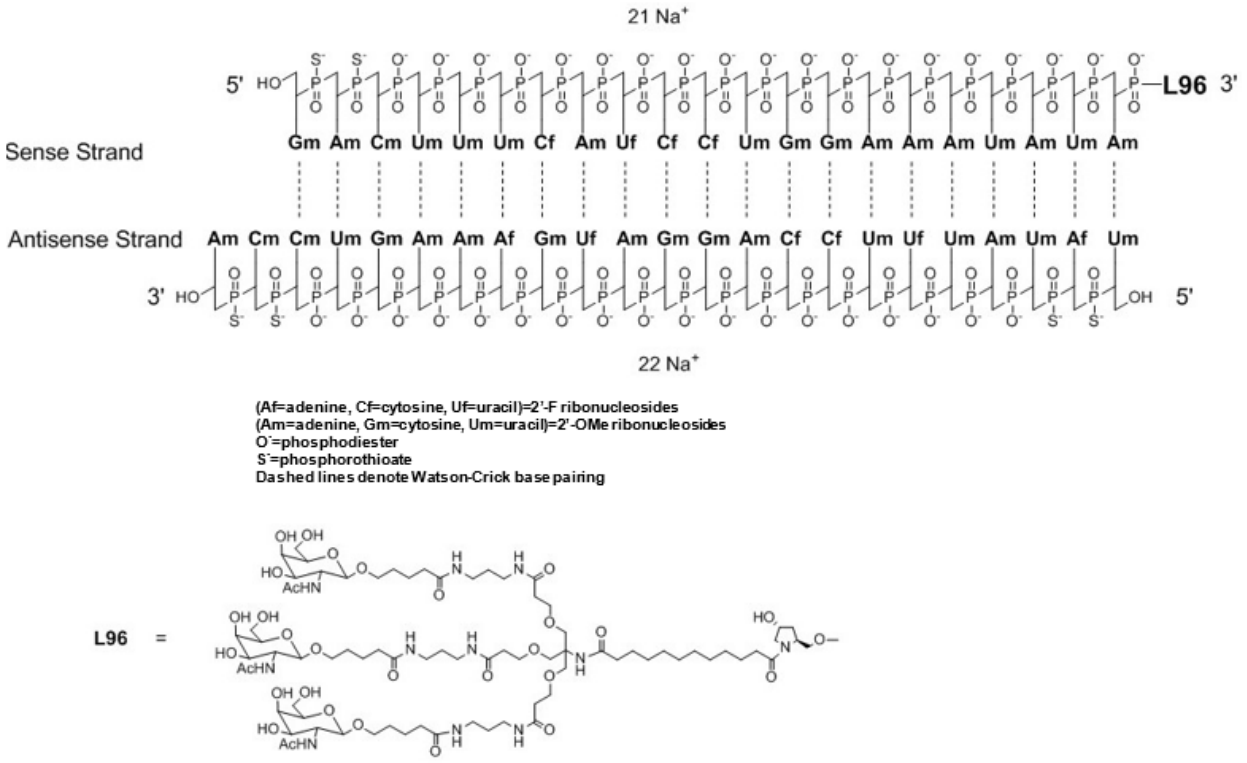
8.7 Renal Impairment

No dose adjustment is necessary in patients with renal impairment including patients with kidney failure treated with hemodialysis *[see Clinical Pharmacology (12.3)]*. OXLUMO has not been studied in patients on peritoneal dialysis.

11 DESCRIPTION

OXLUMO injection contains lumasiran, a *HAO1*-directed double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing *N*-acetylgalactosamine (GalNAc).

The structural formula of lumasiran sodium is presented below:



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 weight is 17,286 Da.

OXLUMO is supplied as a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous administration containing the equivalent of 94.5 mg of lumasiran (provided as lumasiran sodium) in 0.5 mL of water for injection and sodium hydroxide and/or phosphoric acid to adjust the pH to ~ 7.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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 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.

12.2 Pharmacodynamics

The pharmacodynamic effects of OXLUMO have been evaluated in adult and pediatric patients with PH1 across a range of doses and dosing frequency. Dose-dependent reductions in urinary oxalate levels were observed, resulting in the selection of the recommended body weight-based

loading and maintenance dosing regimens. With the recommended dosing regimens, onset of effect was observed within two weeks after the first dose and maximal reductions in urinary oxalate were observed by Month 2 and persisted with continued use of OXLUMO maintenance dosage *[see Figures 1 and 2 in Clinical Studies (14.1, 14.2)]*.

Cardiac Electrophysiology

At the recommended dose, OXLUMO does not lead to clinically relevant QT interval prolongation.

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of OXLUMO were evaluated following administration of single and multiple dosages in patients with PH1 as summarized in Table 3.

Table 3. Pharmacokinetic Parameters of Lumasiran

		Lumasiran
General Information		
Steady-State Exposure	**C_{max} [Median (Range)]**	462 (38.5 to 1500) ng/mL
	$AUC_{0\text{-last}}$ [Median (Range)]	6810 (2890 to 10700) ng·h/mL
Dose Proportionality		• Lumasiran exhibited an approximately dose proportional increase in plasma exposure following single subcutaneous doses ranging from 0.3 to 6 mg/kg. • Lumasiran exhibited time-independent pharmacokinetics with multiple doses of 1 and 3 mg/kg once monthly or 3 mg/kg quarterly.
Accumulation		• No accumulation of lumasiran was observed in plasma after repeated monthly or quarterly dosing.
Absorption		
T_{max} [Median (Range)]		4 (0.5 to 12) hours
Distribution[a]		
Estimated Vd/F		4.9 L
Protein Binding		85%
Elimination		
Apparent Half-Life [Mean (%CV)]		5.2 (47%) hours
Estimated CL/F		26.5 L/hour
Metabolism		
Primary Pathway		Lumasiran is metabolized by endo- and exonucleases to oligonucleotides of shorter lengths.
Excretion		
Primary Pathway		Less than 26% of the administered dose of lumasiran is excreted unchanged into the urine within 24 hours with the rest excreted as inactive metabolite.

[a] Lumasiran distributes primarily to the liver after subcutaneous administration.
C_{max} = maximum plasma concentration; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time of administration (0) to the last measurable time point (last); T_{max} = time to maximum concentration; Vd/F = apparent volume of distribution; CV = coefficient of variation; CL/F = apparent clearance.

Specific Populations

No clinically significant differences in the pharmacokinetics or pharmacodynamics of lumasiran were observed based on age (4 months to < 65 years old), sex, race/ethnicity, renal impairment, use of hemodialysis, or mild to moderate hepatic impairment (total bilirubin ≤ ULN and AST > ULN; or total bilirubin ≤ 3× ULN). The effect of severe hepatic impairment on the pharmacokinetics of lumasiran is unknown.

Body Weight

In children < 20 kg, lumasiran C_{max} was twice as high due to the higher 6 mg/kg dose and faster absorption rate. At the approved recommended dosage, lumasiran AUC was similar across the 6.2 kg to 110 kg body weight range *[see Dosage and Administration (2.1)]*.

Drug Interaction Studies

Clinical Studies

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

In Vitro Studies

In vitro studies indicate that lumasiran is not a substrate or an inhibitor of cytochrome P450 (CYP) enzymes. Lumasiran is not expected to induce CYP enzymes or modulate the activities of drug transporters.

12.6 Immunogenicity

The observed incidence of anti-drug antibody (ADA, including neutralizing antibody) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of OXLUMO or of other siRNA products.

Across all clinical studies in the lumasiran development program, including patients with PH1 and healthy volunteers dosed with OXLUMO, 7 of 120 (6%) lumasiran-treated individuals with mean follow-up duration of 8.9 months, tested positive for ADA, as early as from Day 29.

No clinically significant differences in the safety, pharmacokinetic, or pharmacodynamic profiles of lumasiran were observed in patients who tested positive for ADA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lumasiran was not carcinogenic in transgenic Tg-rasH2 mice following monthly subcutaneous administration of lumasiran for 26 weeks at doses of 150, 500 or 1500 mg/kg. A long-term study to assess carcinogenic risk of lumasiran has not been conducted.

Lumasiran was not genotoxic in an in vitro bacterial reverse mutation (Ames) assay, in the in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes, or the in vivo micronucleus assay in rats.

Administration of lumasiran by weekly subcutaneous doses of 0, 5, 15, and 50 mg/kg in male and female rats prior to and during mating and continuing in females once on Day 6 of presumed gestation resulted in no adverse effects upon the male or female fertility endpoints evaluated.

14 CLINICAL STUDIES

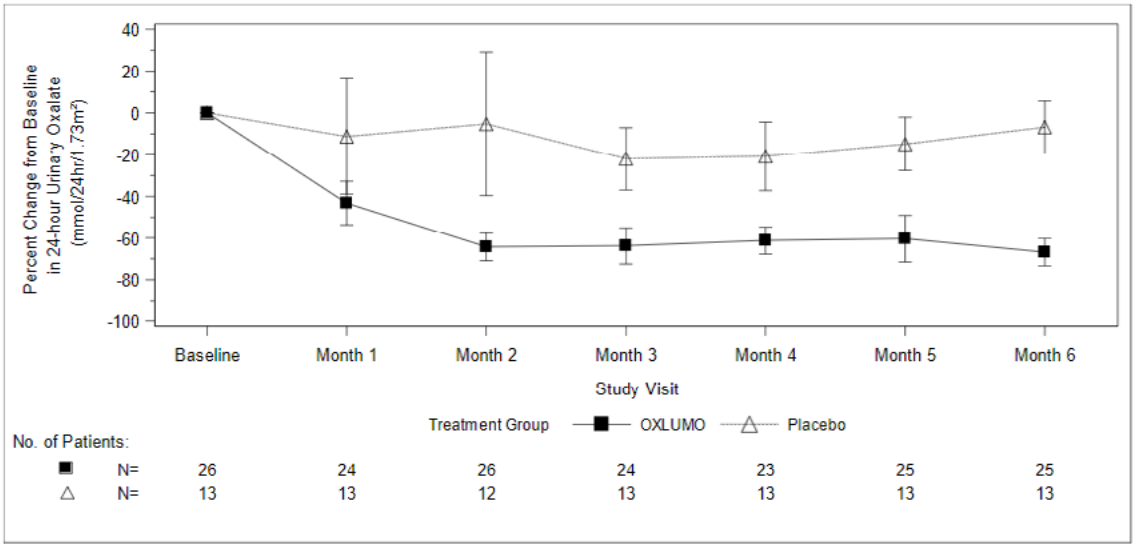
14.1 ILLUMINATE-A

ILLUMINATE-A was a randomized, double-blind trial comparing lumasiran and placebo in 39 patients 6 years of age and older with PH1 and an eGFR ≥30 mL/min/1.73 m^2 (ILLUMINATE-A; NCT03681184). Patients received 3 loading doses of 3 mg/kg OXLUMO (N = 26) or placebo (N = 13) administered once monthly, followed by quarterly maintenance doses of 3 mg/kg OXLUMO or placebo *[see Dosage and Administration (2.1)]*. After six months, all patients received OXLUMO.

The median age of patients at first dose was 15 years (range 6 to 61 years), 67% were male, and 77% were White. At baseline, the median 24-hour urinary oxalate excretion corrected for body surface area (BSA) was 1.7 mmol/24 h/1.73 m^2, the median plasma oxalate level was 13.1 µmol/L, 33% of patients had eGFR ≥90 mL/min/1.73 m^2, 49% had eGFR of 60 to <90 mL/min/1.73 m^2, and 18% had eGFR 30 to <60 mL/min/1.73 m^2, 56% were on pyridoxine, and 85% reported a history of symptomatic kidney stone events.

The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over Months 3 through 6. The LS mean percent change from baseline in 24-hour urinary oxalate in the OXLUMO group was -65% (95% CI: -71, -59) compared with -12% (95% CI: -20, -4) in the placebo group, resulting in a between-group LS mean difference of 53% (95% CI: 45, 62; p<0.0001) [Figure 1].

Figure 1. ILLUMINATE-A: Percent Change from Baseline in 24-hour Urinary Oxalate by Month



Abbreviation: CI = Confidence Interval.
Results are plotted as mean (95% CI) of percent change from baseline.

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). Reduced urinary oxalate levels were maintained through Month 24 in patients treated with OXLUMO.

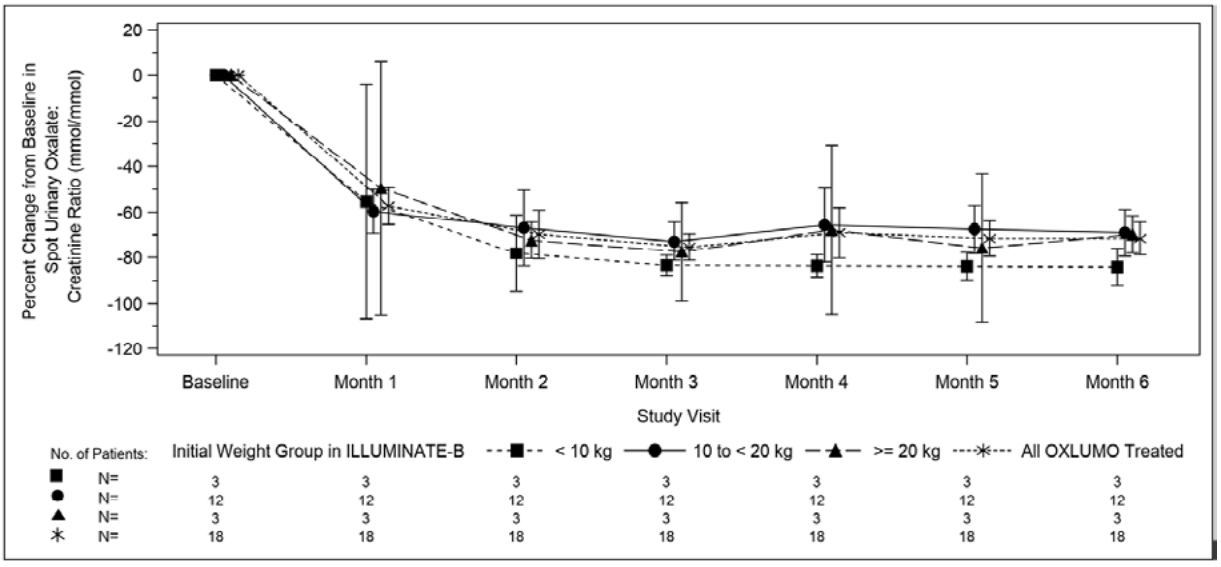
14.2 ILLUMINATE-B

ILLUMINATE-B was a single-arm study in 18 patients <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 (ILLUMINATE-B; NCT03905694). Dosing was based on body weight *[see Dosage and Administration (2.1)]*.

The median age of patients at first dose was 51 months (range 4 to 74 months), 56% were female, and 88% were White. Three patients were less than 10 kg, 12 were 10 kg to < 20 kg, and 3 were ≥ 20 kg. 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. Patients treated with OXLUMO achieved a reduction in spot urinary oxalate: creatinine ratio from baseline of 72% (95% CI: 66, 78) (Figure 2). The reduction in urinary oxalate excretion was maintained with continued OXLUMO treatment through Month 12.

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



Abbreviation: CI = Confidence Interval.
Results are plotted as mean (95% CI) of percent change from baseline.

14.3 ILLUMINATE-C

A total of 21 patients were enrolled and treated with OXLUMO in a multi-center, single-arm study in patients with PH1 and an eGFR ≤ 45 mL/min/1.73 m^2 in patients 12 months of age and older or an elevated serum creatinine for age in patients less than 12 months of age, including patients on

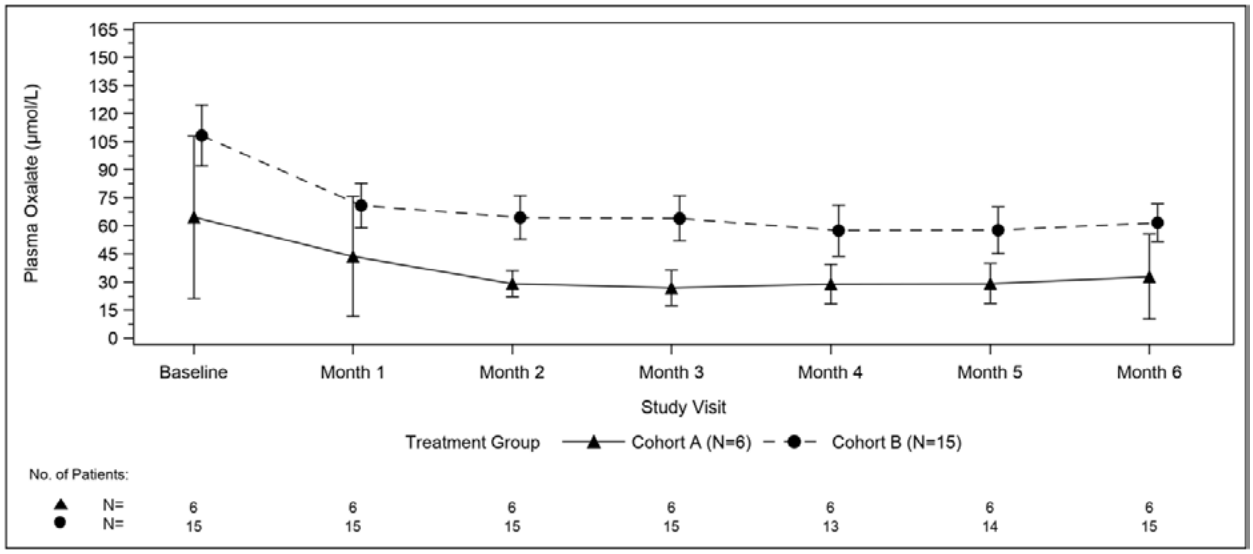
hemodialysis. ILLUMINATE-C included 2 cohorts. Cohort A included 6 patients who did not require dialysis at the time of study enrollment. Cohort B included 15 patients who were on a stable regimen of hemodialysis; the hemodialysis regimen was to remain stable in these patients for the first 6 months of the study. Patients received the recommended dosing regimen of OXLUMO based on body weight *[see Dosage and Administration (3.1)]*. Patients requiring peritoneal dialysis were excluded.

The median age of patients at first dose was 9 years (range 0 to 59 years), 57% were male, and 76% were White. For Cohort A, the median plasma oxalate level was 58 µmol/L. For Cohort B, the median pre-dialysis plasma oxalate level was 104 µmol/L.

The primary endpoint 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). The percent change from baseline to Month 6 in plasma oxalate levels in Cohort A was an LS mean difference of -33% (95% CI: -82, 15) and in Cohort B was -42% (95% CI: -51, -34).

Mean plasma oxalate decreased from 65 µmol/L (95% CI: 21, 108) at baseline to 33 µmol/L (95% CI: 10, 56) at Month 6 in Cohort A, and from 108 µmol/L (95% CI: 92, 125) at baseline to 62 µmol/L (95% CI: 51, 72) at Month 6 in Cohort B. The time course for changes in plasma oxalate is shown in Figure 3.

Figure 3. ILLUMINATE-C: Plasma Oxalate Levels (µmol/L) during the Primary Analysis Period by Month



Abbreviation: CI = Confidence Interval.
Results are plotted as mean (95% CI) of actual values.
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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

OXLUMO is a clear, colorless-to-yellow solution available in single-dose vials of 94.5 mg/0.5 mL in cartons containing one vial (NDC 71336-1002-1).

16.2 Storage and Handling

Store at 2°C to 25°C [36°F to 77°F].

Store OXLUMO in its original container until ready for use.

Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142