



BILLING AND CODING GUIDE

Physician Office

Please see [Important Safety Information](#) on page 7
and full [Prescribing Information](#).

Coverage, coding, and payment in the physician office^a

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.

Coverage

- **For Medicare Patients** receiving OXLUMO who are covered under **Medicare Part B**, the Medicare Administrative Contractors (MACs) may require additional documentation to determine the medical necessity of the treatment, although prior authorization is not required^{a,b}
- **For patients enrolled in a Medicaid or commercial health plan**, OXLUMO coverage will vary by payer

Payment

Payer Type	Payment Methodology
Medicare Fee-for-Service	Average sales price (ASP) + 6% ^{c,d}
State Medicaid and Commercial Payers	Payment rates will vary by payer and provider contract

^aIt is always the provider’s responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact payers for specific information on their coding, coverage, and payment policies.

^bMedicare Advantage plans may require prior authorization for OXLUMO.

^cOXLUMO will be reimbursed based on ASP in the Hospital Outpatient Department (HOPD) setting. However, since OXLUMO is not included in the ASP File, then in the non-HOPD setting (e.g., physician office), the payment amount will be determined by the individual MACs. Each MAC has the option to either set the payment amount itself based on WAC, or request the payment amount from Centers for Medicare and Medicaid Services (CMS).

^dDoes not account for any required payment reductions if sequestration is in effect.

Anylam Field Reimbursement Directors are available to meet with you and your staff to answer coverage and reimbursement questions about OXLUMO. Contact Anylam Assist[®] at 1-833-256-2748.

Please see [Important Safety Information](#) on page 7 and full [Prescribing Information](#).



Coding^a

Please refer to the table below to support appropriate claims submission for OXLUMO® (lumasiran).

Code Type	Code	Code Description
ICD-10-CM	E72.53	Primary hyperoxaluria
CPT ^b	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS ^c	J0224	Injection, lumasiran, 0.5 mg
NDC	10-digit: 71336-1002-1 11-digit: 71336-1002-01	94.5 mg / 0.5 mL single-dose vial

^aIt is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact payers for specific information on their coding, coverage, and payment policies.

^bCPT Copyright 2019 American Medical Association. All rights reserved.
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Applicable FARS/DFARS Restrictions Apply to Government Use.

Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

^cHCPCS codes for OXLUMO will vary for dates of service prior to July 1, 2021.

ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; CPT=Current Procedural Terminology; HCPCS=Healthcare Common Procedure Coding System; NDC=National Drug Code.

Providers should consult the ICD-10-CM code book and use their own clinical judgment to confirm coding.

Please see [Important Safety Information](#) on page 7 and full [Prescribing Information](#).

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

Physician office: sample CMS-1500 claim form

OXLUMO® (lumasiran) and the associated services provided in a physician office are billed on the CMS-1500 claim form or its electronic equivalent. A sample CMS-1500 claim form for billing OXLUMO is provided on the next page.

- The following CMS-1500 claim form for OXLUMO is for illustrative purposes
- It is the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for the products and services rendered
- Providers should contact payers for specific information on their coding, coverage, and payment policies
- Payers may limit the charges on a single claim, rejecting claims over the specified limit. Providers should contact payers for information on claim charge limits and claims submission guidance
- Medicare claims require the use of the JW (drug amount discarded/not administered to any patient) or JZ (zero drug amount discarded/not administered to any patient) modifiers when applicable
 - Effective for dates of service on or after January 1, 2017, Medicare requires the use of the JW modifier on any claims for single-use vials when there is discarded drug
 - Effective for dates of service on or after July 1, 2023, Medicare requires the use of the new JZ modifier on any claims for single-use vials when there are no discarded drug amount
 - Wastage-reporting policies for payers other than Medicare may vary. Providers should check with their specific plans about policies related to billing for discarded drug and use of the JW and JZ modifiers
- Providers should contact their billing software vendors to ensure that they are utilizing the recommended loops and segments

Please see [Important Safety Information](#) on page 7 and full [Prescribing Information](#).



LOCATOR 21

Enter the appropriate primary diagnosis code from the patient's medical record in Locator 21A.

LOCATOR 21

Enter "0" to indicate use of ICD-10-CM diagnosis coding system.

LOCATOR 24_{A-B}

Enter the date of service and the appropriate place of service code.

LOCATOR 24

Enter the OXLUMO® (lumasiran) HCPCS code J0224 on the first line and the CPT code 96372 for drug administration on the second line.

Sample CMS-1500 Claim Form

The image shows a sample CMS-1500 Claim Form with several annotations. A green box labeled 'LOCATOR 21' points to the 'PATIENT'S NAME (Last Name, First Name, Middle Initial)' field. Another green box labeled 'LOCATOR 21 ICD-IND' points to the 'ICD-IND' field. A third green box labeled 'LOCATOR 24_{A-B}' points to the 'DATE OF SERVICE' and 'PLACE OF SERVICE' fields. A fourth green box labeled 'LOCATOR 24' points to the 'DIAGNOSIS OR NATURE OF ILLNESS OR INJURY' field. A fifth green box labeled 'LOCATOR 24_D' points to the 'DATE OF SERVICE' field. A sixth green box labeled 'LOCATOR 24_G' points to the 'NUMBER OF SERVICE UNITS' field. A seventh green box labeled 'LOCATOR 24_E' points to the 'DIAGNOSIS OR NATURE OF ILLNESS OR INJURY' field. The form includes fields for patient information, insurance information, and service details. The bottom of the form has a 'PLEASE PRINT OR TYPE' section and a 'Clear Form' button.

LOCATOR 24_D

Enter the appropriate HCPCS code for OXLUMO: J0224 (injection, lumasiran, 0.5 mg)

Shaded area of Locator 24D (when applicable): N471336100201 MLX (X = number of ML: for example ML0.5 = 1 vial, ML1 = 2 vials, etc.)

Note: HCPCS codes for OXLUMO will vary for dates of service prior to July 1, 2021.

LOCATOR 24_G

Enter the number of service units for each line item.






LOCATOR 24_E

Specify the diagnosis, from Locator 21, that relates to the product or procedure listed in Locator 24D.

Please see [Important Safety Information](#) on page 7 and full [Prescribing Information](#).

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

Clean claim filing checklist

-  Select the appropriate primary diagnosis
-  Confirm appropriate clinical documentation to support the diagnosis
-  Understand any payer-specific requirements (prior authorization, coding details, etc)
- 
 - Utilize all appropriate ICD-10-CM, CPT®, and HCPCS codes
 - For all claims in the physician office setting, use HCPCS J0224 (Injection, lumasiran, 0.5 mg) for dates of service on or after July 1, 2021^a
 - Remember: Billing unit = 0.5 mg
 - Remember to use the sample claim form on page 5 as a guide
-  Anticipate requests from payers for additional clinical information prior to claims being processed for payment

It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for those products and services rendered. Contact third-party payers for specific information on their coding and payment policies.

^aHCPCS codes for OXLUMO® (lumasiran) may vary for dates of service prior to July 1, 2021.

Please see [Important Safety Information](#) on page 7 and full [Prescribing Information](#).

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



Monday–Friday, 8AM–6PM
☎: 1-833-256-2748 | 📠: 1-833-256-2747

To learn more about OXLUMO® (lumasiran),
visit www.OXLUMOHCP.com.

INDICATION

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

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common ($\geq 20\%$) adverse reaction reported in patients treated with OXLUMO was injection site reaction. Injection site reactions included erythema, swelling, pain, hematoma, pruritus, and discoloration.

Pregnancy and Lactation

No data are available on the use of OXLUMO in pregnant women. No data are available on the presence of OXLUMO in human milk or its effects on breastfed infants or milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for OXLUMO and any potential adverse effects on the breastfed child from OXLUMO or the underlying maternal condition.

For additional information about OXLUMO, please see full [Prescribing Information](#).

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 *HAOI*-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: 09/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 m² 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 ≥ 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 $1.5 \times \text{ULN}$ or $\text{AST} > \text{ULN}$] or moderate hepatic impairment (total bilirubin > 1.5 to $3 \times \text{ULN}$ with any AST). OXLUMO has not been studied in patients with severe hepatic impairment (total bilirubin > $3 \times \text{ULN}$ with any AST) [see *Clinical Pharmacology* (12.3)].

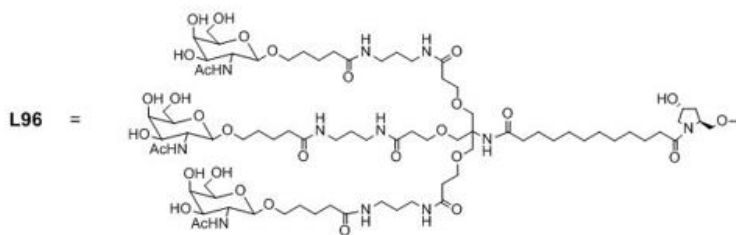
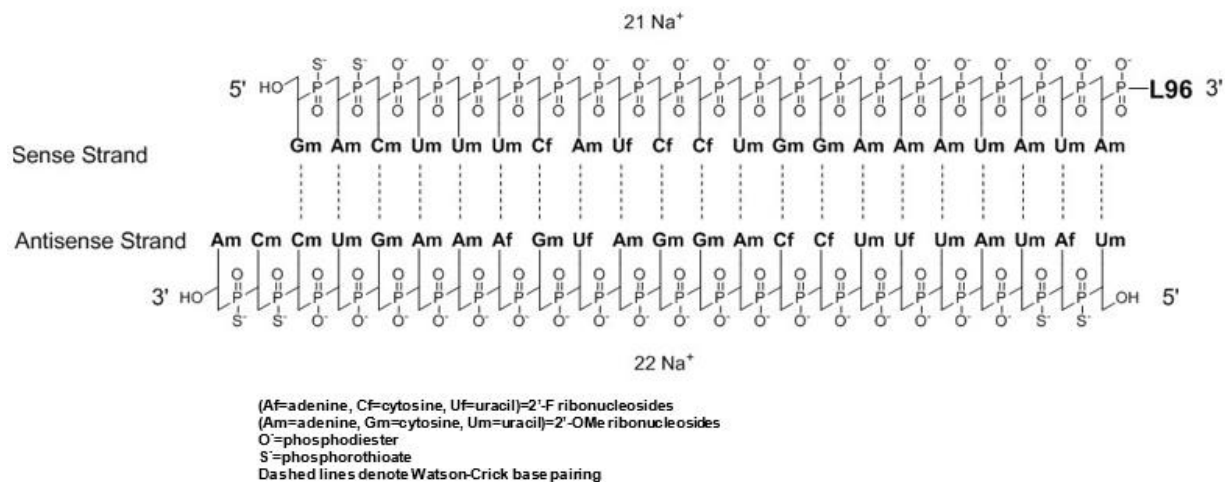
8.7 Renal Impairment

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 *HAOI*-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 (*HAOI*) 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-last} [Median (Range)]	6810 (2890 to 10700) ng·h/mL
Dose Proportionality		<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> 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-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 \leq ULN and AST $>$ ULN; or total bilirubin $\leq 3 \times$ 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

Carcinogenicity studies were conducted in Tg-rasH2 mice and Sprague Dawley rats.

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.

In a 2-year carcinogenicity study, lumasiran was not carcinogenic up to the highest dose tested. Sprague Dawley rats were administered subcutaneous doses of 20, 55, or 110 mg/kg lumasiran once every 4 weeks (3, 9, or 18 times the normalized maintenance MRHD, based on body surface area).

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

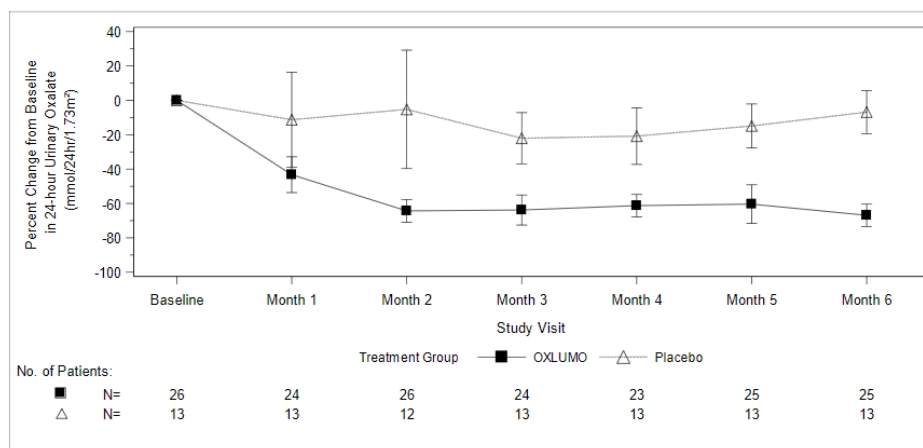
14.1 ILLUMINATE-A

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 m² (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 m², the median plasma oxalate level was 13.1 μ mol/L, 33% of patients had eGFR ≥ 90 mL/min/1.73 m², 49% had eGFR of 60 to <90 mL/min/1.73 m², and 18% had eGFR 30 to <60 mL/min/1.73 m², 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 m²) 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.

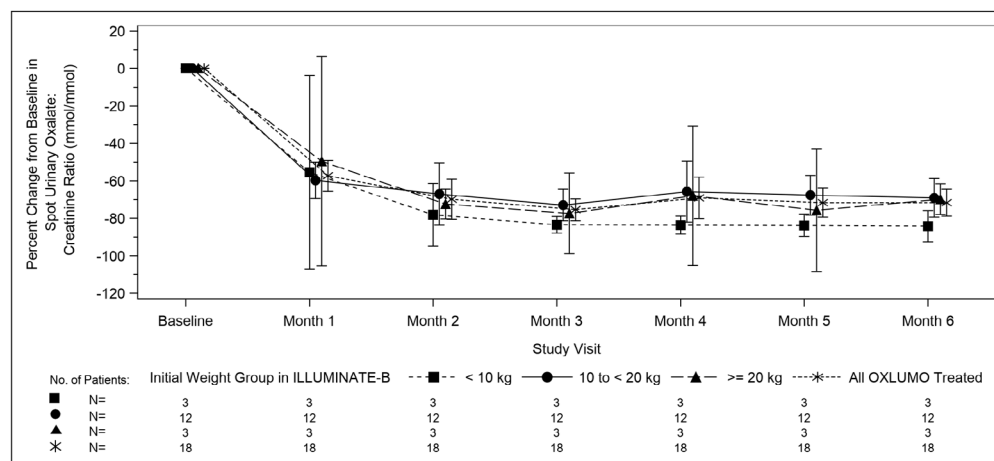
14.2 ILLUMINATE-B

ILLUMINATE-B was a single-arm study in 18 patients <6 years of age with PH1 and an eGFR >45 mL/min/1.73 m² 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

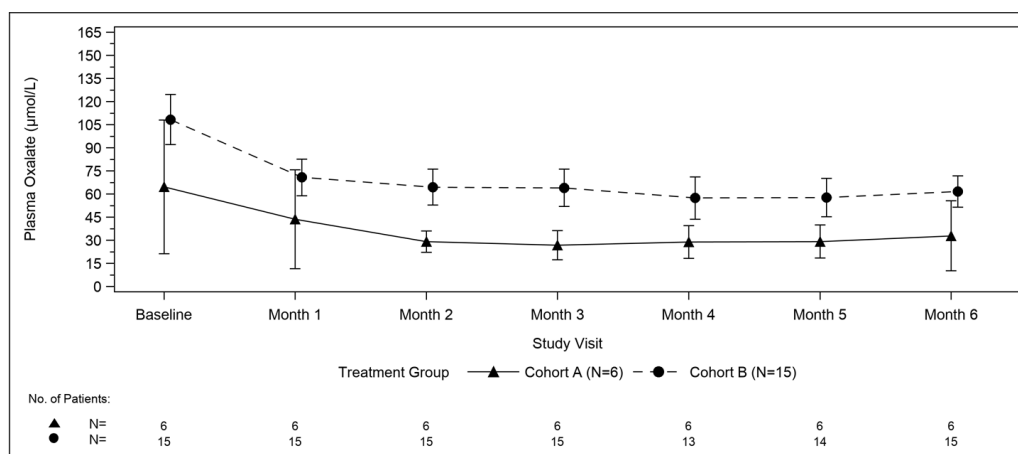
A total of 21 patients were enrolled and treated with OXLUMO in a multi-center, single-arm study in patients with PH1 and an eGFR ≤ 45 mL/min/1.73 m² in patients 12 months of age and older or an elevated serum creatinine for age in patients less than 12 months of age, including patients on hemodialysis. 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* (2.1)]. 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 μ mol/L. For Cohort B, the median pre-dialysis plasma oxalate level was 104 μ mol/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 μ mol/L (95% CI: 21, 108) at baseline to 33 μ mol/L (95% CI: 10, 56) at Month 6 in Cohort A, and from 108 μ mol/L (95% CI: 92, 125) at baseline to 62 μ mol/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