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

Start Form

Alnylam ASSIST

▷ Before submitting the Start Form to Alnylam Assist™, patient **and** prescriber signatures are required
▷ **Patients currently prescribed an Alnylam medicine who are enrolled in Alnylam Assist do not need to complete Sections 1 – 5**

For Patients

Alnylam Assist™ Enrollment

(Sections 1 – 5 to be read and completed by **Patient** or **Patient's Authorized Representative**)

The purpose of this form is to permit Alnylam Assist™ participants to receive additional information and support ("Patient Support") from Alnylam Pharmaceuticals, Inc., its affiliates, representatives, agents, and contractors ("Alnylam"). Alnylam Assist™ provides Patient Support to eligible patients who have been prescribed an Alnylam medicine. This includes: (1) providing reimbursement and financial support to eligible patients (such as investigating your insurance coverage, confirming out-of-pocket costs, and reviewing eligibility for financial assistance); (2) working with you and your provider to fill your prescription; and (3) providing you with disease and medication-related educational resources and communications. Your authorization in this form will relate to information and support with respect to any Alnylam medicine you have been prescribed or may be prescribed in the future.

Please read this form carefully and ask any questions that you may have before signing.

1. Patient Information

Name (First, MI, Last):			
Date of Birth: Month/Day/Year		Email:	
Street Address:			
City:		State:	ZIP:
Home Phone #: ☐ **Preferred** ☐ **Okay to leave message**	Mobile Phone #: ☐ **Preferred** ☐ **Okay to leave message**	Alternative Phone # (if available): ☐ **Preferred** ☐ **Okay to leave message**	
Caregiver Name (optional):	Caregiver Relationship to Patient (optional):	Caregiver Phone (optional): ☐ **Okay to leave message**	
Caregiver Email (optional):	Language translation? ☐ Yes, translation needed ☐ No If yes, please indicate language:		

2. Insurance Information

Attach a copy of both sides of your INSURANCE and PRESCRIPTION cards ☐ **Check if you do not have insurance**

Primary Insurance Provider:	Employer Name:	Policy Number:		Group Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year		Insurance Phone:
Pharmacy Plan Provider (if applicable):	Policy Number:	Group Number:	Rx Bin Number:	Rx PCN Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year		Insurance Phone:
Secondary Insurance Provider (if applicable):	Employer Name:	Policy Number:		Group Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year		Insurance Phone:

▷ Continue to page 2 to complete the patient portion of the Start Form

3. Authorization to Share Protected Health Information

By signing below, I authorize my healthcare providers, including my physicians and pharmacies ("My Providers") and my health insurance plan ("My Plan") to share my medical information (such as information about my diagnosis, prescriptions, and treatment) and my insurance information ("My Information") with Alnylam so that Alnylam can provide Patient Support. I authorize My Providers to use My Information to provide me with certain offerings related to my treatment and any Alnylam medicine My Providers may prescribe for me at any time. I understand that my pharmacy will receive payment from Alnylam for disclosing My Information to Alnylam. I understand that once My Information has been disclosed, federal privacy laws may no longer protect the information. However, I understand that Alnylam agrees to protect My Information by using and disclosing it only for purposes described in this Authorization or as required by law. I understand that I may refuse to sign this Authorization, and that my treatment, insurance enrollment, and eligibility for insurance benefits are not conditioned upon signing this Authorization. I also understand, however, that refusing to sign this Authorization means that I may not participate in Alnylam Assist™ and may not be able to take advantage of other offerings by Alnylam. I may cancel or revoke this Authorization at any time by mailing a letter to Privacy Officer at Alnylam, Attn: Legal Department, 675 West Kendall Street, Cambridge, MA 02142 or by sending an email to privacy@alnylam.com. I understand that if I revoke this Authorization, My Providers and Alnylam will stop using and sharing My Information under this Authorization, but my revocation will not affect uses and disclosures of My Information prior to my revocation in reliance upon this Authorization.

This Authorization expires ten (10) years from the date signed below, or earlier if required by state or local law, unless I revoke it before then. I understand that I may receive a copy of this Authorization.

Print Patient or Authorized Patient Representative Name	X Signature of Patient or Authorized Patient Representative
Relationship to Patient	Date

4. Authorization for Alnylam Assist™ and Communications

By signing below, I confirm I would like to enroll in the Alnylam Assist™ program and authorize Alnylam to provide me with Patient Support. I understand that Alnylam Assist™ is an optional program.

I agree that Alnylam may use My Information and share it with My Providers or My Plan in connection with providing the Patient Support, administering the Alnylam Assist™ program, or as otherwise required by Alnylam to meet its legal obligations. For example, Alnylam may communicate with me (such as by mail, phone, email, and/or text message) or my caregiver, use My Information to tailor the Alnylam Assist™-related communications to my needs, and share information with My Providers about dispensing Alnylam medicine to me. I understand that Alnylam may de-identify My Information, combine it with information about other patients, and use the resulting information for Alnylam's business purposes.

Print Patient or Authorized Patient Representative Name	X Signature of Patient or Authorized Patient Representative
Relationship to Patient	Date

5. Opt-In to Receive Marketing Communications (optional)

☐ By checking this box, I authorize Alnylam, and companies working with Alnylam, to contact me by mail, email, fax, and/or telephone regarding marketing and promotional communications, customer surveys, or for market research surveys. **I understand that I am not required to provide this consent as a condition of receiving any Alnylam medicine or services from Alnylam.**

Please see Important Safety Information on page 4, and full Prescribing Information.

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

Start Form

Alnylam ASSIST

For Healthcare Providers

(Sections 6 – 8 to be read and completed by **Healthcare Provider**)

6. Prescriber Information

Name (First, Last):			Office/Clinic/Institution Name:	Specialty:
Practice Street Address:			City: State:	ZIP:
Phone:	Fax:	Tax ID #:	National Provider ID (NPI) #:	State License #:
Office Contact Name:			Phone:	Email:

Product Acquisition:

- ☐ Specialty Pharmacy: ○ Orsini ○ PANTHERx ○ No preference
- ☐ Specialty Distributor (McKesson Specialty or McKesson Plasma and Biologics)
- ☐ Unknown

Anticipated First Treatment Date:

7. OXLUMO® (lumasiran) Prescription (This is a prescription; a prescriber's signature and date are required.)

Full Patient Name (First, Last and Middle Initial):

Patient Date of Birth: Month/Day/Year:

Primary Diagnosis Code:

	Treatment	Patient Weight (in kg)	Date Patient Weight Taken	Body Weight	OXLUMO Prescription	Total Calculated Dose	Number of Vials/Treatment	Refills
OXLUMO Injection for subcutaneous use, 94.5 mg/0.5 mL	Starting Dose (given at 1-month intervals)			☐ Less than 10 kg	☐ 6 mg/kg once monthly for 3 doses	(mg) _____ (mL) _____	____ 94.5 mg/0.5 mL vial(s)	☐ Refill x 2 ☐ Other___
				☐ 10 kg to less than 20 kg	☐ 6 mg/kg once monthly for 3 doses			
				☐ 20 kg and above	☐ 3 mg/kg once monthly for 3 doses			
	Ongoing Dose (begin 1 month after the last starting dose)			☐ Less than 10 kg	☐ 3 mg/kg once monthly	(mg) _____ (mL) _____	____ 94.5 mg/0.5 mL vial(s)	☐ Refill x 8 ☐ Refill x 2 ☐ Other___
				☐ 10 kg to less than 20 kg	☐ 6 mg/kg once every 3 months (quarterly)			
				☐ 20 kg and above	☐ 3 mg/kg once every 3 months (quarterly)			

Any known allergies? ☐ Yes ☐ No If yes, please list:

List or attach a list of concomitant medications:

Special Instructions:

☐ If acquiring through Orsini or PANTHERx, please check here to authorize ancillary supplies, such as needles and syringes, as needed to administer treatment.

☐ I confirm that my patient is being prescribed OXLUMO for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in children and adults.

I authorize Alnylam to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy.
I will comply with my state-specific prescription requirements, such as e-prescribing, state-specific prescription form, fax language, etc.

X _____ _____

Prescriber Signature (No Stamps) Dispense as Written — Date

X _____ _____

Prescriber Signature (No Stamps) Substitution Permitted — Date

Desired Site of Care _____

- ☐ Home Injection (see patient home address)
- ☐ Alternate Medical Facility (provide facility name and address)
- ☐ Physician Office (see provider office address)
- ☐ Facility to Home (first dose at facility; remainder at home)

Facility Name/Address _____

▷ Continue to page 4 to complete the prescriber portion of the Start Form

Please see Important Safety Information on page 4, and full Prescribing Information.

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

Alnylam ASSIST

8. Prescriber Declaration

By signing below, I certify that:

- ▷ The information contained in this form is complete and accurate to the best of my knowledge
- ▷ I understand that Alnylam is not responsible for filing claims or submitting other information to my patient's insurer and that the information provided by Alnylam Assist™ is educational in nature
- ▷ I understand that my patient may authorize Alnylam Assist™ to provide Patient Support. I understand that this program does not include individual treatment or medical advice to the patient, and it does not replace the medical treatment and care provided by me as the patient's healthcare provider
- ▷ I further certify that I understand that any support provided by Alnylam Assist™ on behalf of any patient is not made in exchange for any express or implied agreement or understanding that I would recommend, prescribe, or use OXLUMO® (lumasiran) or any other Alnylam product, and any decision to prescribe OXLUMO was, and in the future will be, based solely on my determination of medical necessity
- ▷ I have obtained the required authorizations from my patient to release the referenced medical and/or other patient information relating to my patient's treatment to Alnylam Assist™

x	
Prescriber signature (stamps not acceptable)	Date

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 (≥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.

Fax the completed Start Form to 1-833-256-2747 | Call Alnylam Assist™ at 1-833-256-2748 8AM–6PM, Monday–Friday | For more information, visit www.AlnylamAssist.com

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)]*.

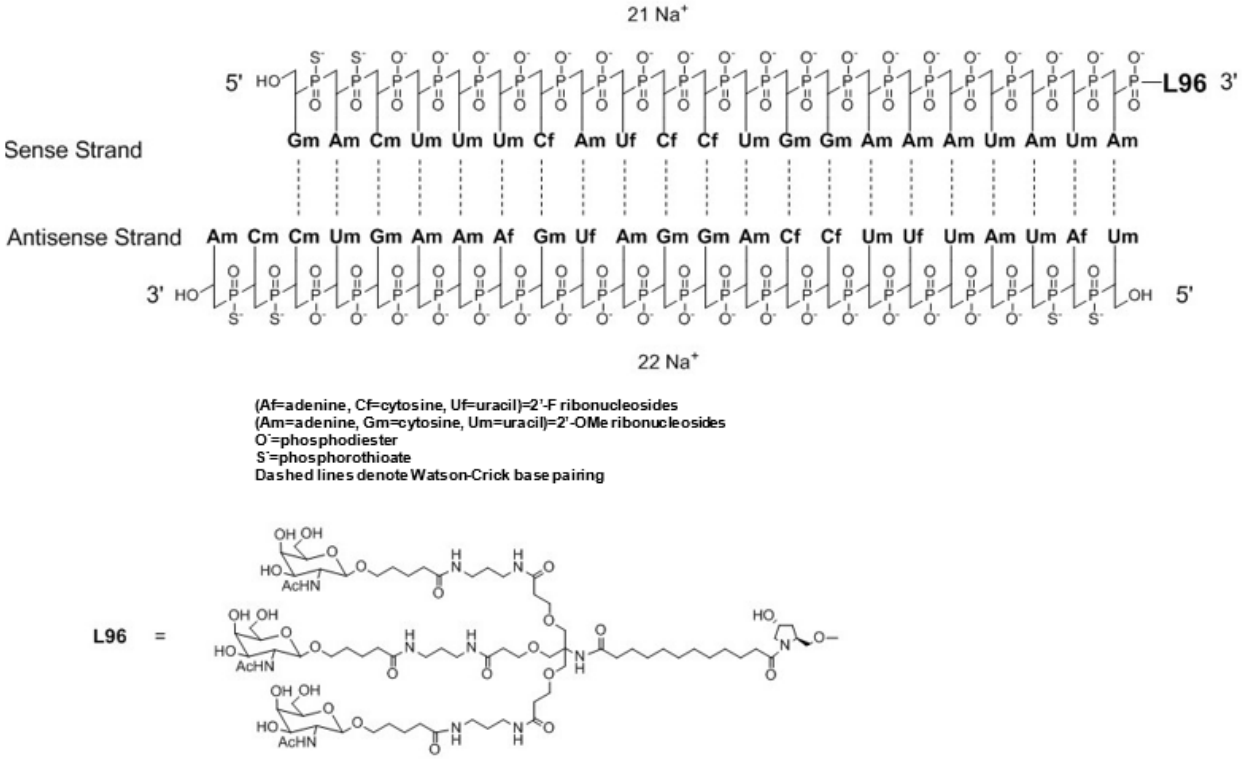
8.7 Renal Impairment

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

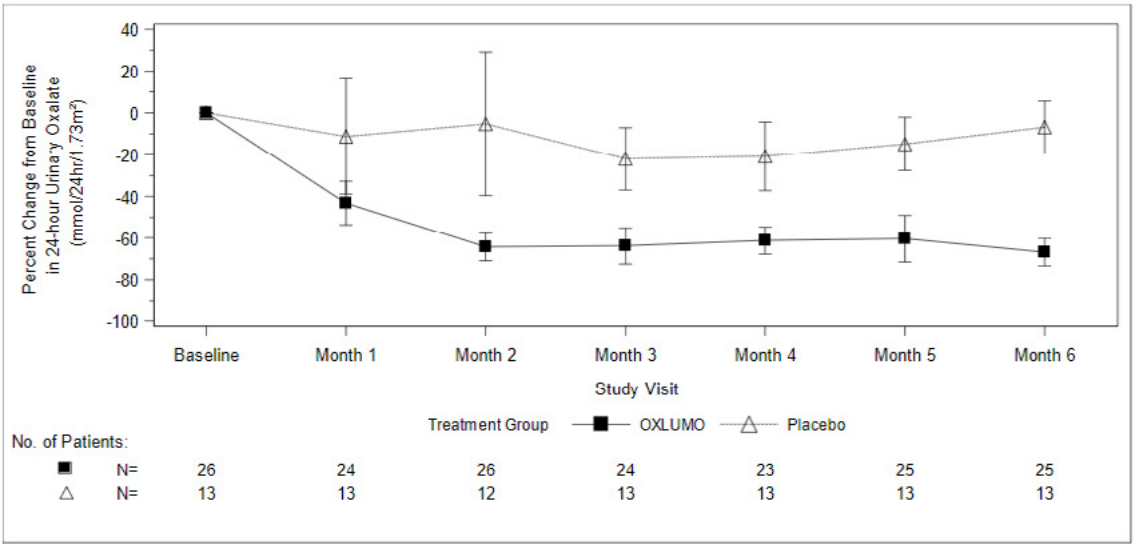
14.1 ILLUMINATE-A

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.

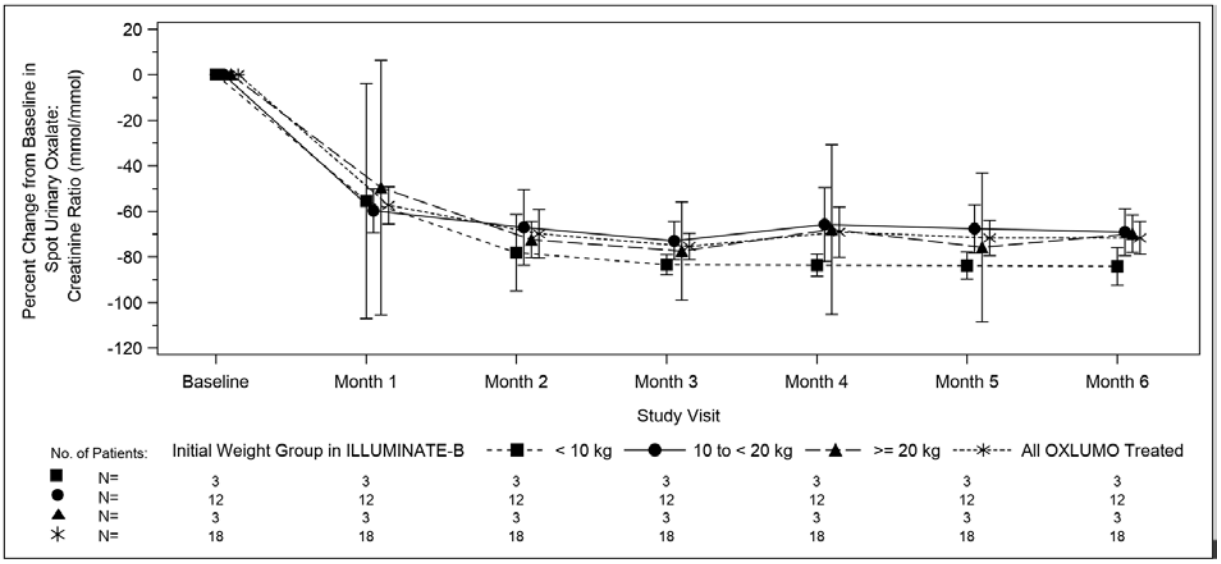
14.2 ILLUMINATE-B

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

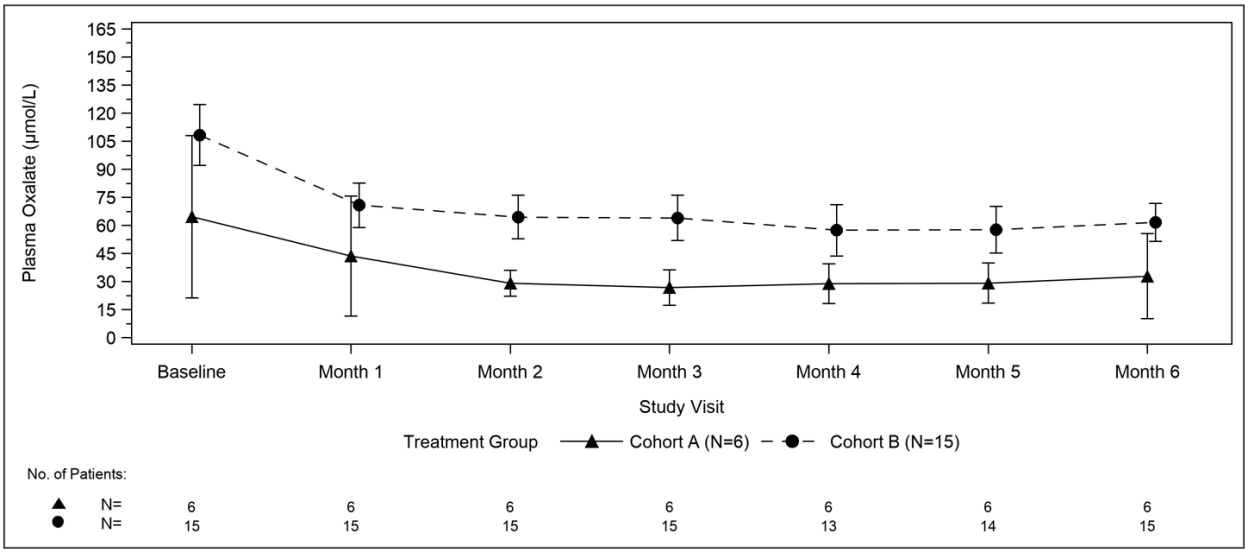
hemodialysis. ILLUMINATE-C included 2 cohorts. Cohort A included 6 patients who did not require dialysis at the time of study enrollment. Cohort B included 15 patients who were on a stable regimen of hemodialysis; the hemodialysis regimen was to remain stable in these patients for the first 6 months 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