

▶ Before submitting the Start Form to Anylam Assist®, patient **and** prescriber signatures are required

For Patients Anylam 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 Anylam Assist® participants to receive information and support (“Patient Support”) from Anylam Pharmaceuticals, Inc., its affiliates, representatives, agents, and contractors (“Anylam”). Anylam Assist® provides Patient Support to eligible patients who have been prescribed an Anylam medicine. This includes: (1) providing reimbursement and financial support (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 communications.

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

1. Patient Information

Name (First, MI, Last):		Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female	
Date of Birth: Month/Day/Year	Email:		
Street Address:			
City:	State:	ZIP:	
Preferred Phone Number: <input type="checkbox"/> Okay to leave voicemail		Alternative Phone Number (if different from preferred): <input type="checkbox"/> Okay to leave voicemail	
Caregiver Name (optional):	Caregiver Relationship to Patient (optional):	Caregiver Phone (optional):	
Language translation? <input type="checkbox"/> Yes, translation needed <input type="checkbox"/> 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:	

Please see [Important Safety Information](#) on page 4, and full [Prescribing Information](#).

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 Anylam so that Anylam can provide Patient Support. I authorize My Providers to use My Information to provide me with certain offerings related to my medication and treatment. I understand that my pharmacy will receive payment from Anylam for disclosing My Information to Anylam. I understand that once My Information has been disclosed, federal privacy laws may no longer protect the information. However, I understand that Anylam agrees to protect My Information by using and disclosing it only for purposes described in this Authorization or as required by law or regulations. 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 Anylam Assist® and may not be able to take advantage of other offerings by Anylam. I may cancel or revoke this Authorization at any time by mailing a letter to Privacy Officer at Anylam, Attn: Legal Department, 675 West Kendall Street, Cambridge, MA 02142 or by sending an email to privacy@anylam.com. I understand that if I revoke this Authorization, My Providers and Anylam 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.

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

4. Authorization for Anylam Assist® and Communications

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

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

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

5. Opt In to Receive Marketing Communications (optional)

Anylam would like to contact you regarding Anylam’s medicines or Anylam information that may be of interest to you.

Email (if not included above) _____

By checking this box, I authorize Anylam, and companies working with Anylam, to contact me by mail, email, fax, and/or telephone regarding other potential topics of interest to me, surveys, or occasionally for market research purposes. **I understand that I am not required to provide this consent as a condition of receiving any Anylam medicine or services from Anylam.**

Please see [Important Safety Information](#) on page 4, and full [Prescribing Information](#).

For Healthcare Providers

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

6. Prescriber Information

Name (First, Last):				Practice Name:	Specialty:
Practice Street Address:				City:	State:
ZIP:	Phone:	Fax:	National Provider ID (NPI) #:	State License #:	
Office Contact Name:			Phone:	Email:	
Product acquisition: <input type="checkbox"/> Specialty Pharmacy: <input type="radio"/> Orsini <input type="radio"/> PANTHERx <input type="radio"/> No preference <input type="checkbox"/> Specialty Distributor (McKesson Specialty or McKesson Plasma and Biologics) <input type="checkbox"/> Unknown				Anticipated First Treatment Date:	

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

Patient Name:	Date of Birth: Month/Day/Year:
---------------	--------------------------------

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

Primary Diagnosis Code:

	Treatment	Patient Weight (in kg)	Date Patient Weight Taken	Body Weight	OXLUMO Prescription	Total Calculated Dose	Number of Vials Needed	Refills
OXLUMO Injection for subcutaneous use, 94.5 mg/0.5 mL	Starting Dose (given at 1-month intervals)			<input type="checkbox"/> Less than 10 kg	<input type="checkbox"/> 6 mg/kg once monthly for 3 doses	(mg) _____	94.5 mg/0.5 mL vial(s)	<input type="checkbox"/> Refill x 2 <input type="checkbox"/> Other ___
				<input type="checkbox"/> 10 kg to less than 20 kg	<input type="checkbox"/> 6 mg/kg once monthly for 3 doses	(mL) _____		
				<input type="checkbox"/> 20 kg and above	<input type="checkbox"/> 3 mg/kg once monthly for 3 doses			
	Ongoing Dose (begin 1 month after the last starting dose)			<input type="checkbox"/> Less than 10 kg	<input type="checkbox"/> 3 mg/kg once monthly	(mg) _____	94.5 mg/0.5 mL vial(s)	<input type="checkbox"/> Refill x 8 <input type="checkbox"/> Refill x 2 <input type="checkbox"/> Other ___
				<input type="checkbox"/> 10 kg to less than 20 kg	<input type="checkbox"/> 6 mg/kg once every 3 months (quarterly)	(mL) _____		
				<input type="checkbox"/> 20 kg and above	<input type="checkbox"/> 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 authorize Anylam to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy designated by the patient. 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) Physician Office (see provider office address)
 Alternate Medical Facility (provide facility name and address) Facility to Home (first dose at facility; remainder at home)

Facility Name/Address _____

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 Alylam is not responsible for filing claims or submitting other information to my patient's insurer and that the information provided by Alylam Assist[®] is advisory in nature
- ▷ I understand that my patient may authorize Alylam 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 service provided by Alylam 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 Alylam 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 Alylam 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 oxalate levels in children and adults.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reaction that occurred in patients treated with OXLUMO was injection site reaction (38%). Symptoms included erythema, pain, pruritus, and swelling.

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 Alylam Assist[®] at 1-833-256-2748
8AM–6PM ET, Monday–Friday

For more information,
visit www.AlylamAssist.com

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

-----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 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 (begin 1 month after the last loading dose)
less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

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: 11/2020

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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 oxalate levels in pediatric and adult patients [see *Clinical Pharmacology (12.1)*, *Clinical Studies (14.1, 14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosing regimen of OXLUMO consists of loading doses followed by maintenance doses 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 (begin 1 month after the last loading dose)
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

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 data reflect placebo-controlled and open-label clinical studies in 77 patients with PH1 (including 56 pediatric patients). Patients ranged in age from 4 months to 61 years at first dose. The median duration of exposure was 9.1 months (range 1.9 to 21.7 months). Overall, 58 patients were treated for at least 6 months, and 18 patients for at least 12 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. The most common ($\geq 20\%$) adverse reaction reported was injection site reaction. Injection site reactions occurred throughout the study period and included erythema, pain, pruritus, and swelling. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment.

In the single-arm study (ILLUMINATE-B) in patients with PH1 who are < 6 years of age, the safety profile observed was similar to that seen in ILLUMINATE-A [see *Clinical Studies (14)*].

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		

6.2 Immunogenicity

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

Across all clinical studies in the lumasiran development program, including patients with PH1 and healthy volunteers dosed with OXLUMO, 6 of 100 (6%) lumasiran-treated individuals with mean follow-up duration of 8.9 months, tested positive for anti-drug antibodies (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 anti-lumasiran antibody.

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 children 6 years or older and adults with PH1 (ILLUMINATE-A), and a single-arm clinical study in children less than 6 years of age with PH1 (ILLUMINATE-B) [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 $1.5 \times$ ULN or AST $>$ ULN) or moderate hepatic impairment (total bilirubin >1.5 – $3 \times$ ULN with any AST). OXLUMO has not been studied in patients with severe hepatic impairment (total bilirubin $>3 \times$ ULN with any AST) [see *Clinical Pharmacology (12.3)*].

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		
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, eGFR 30 to < 90 mL/min/1.73 m², or mild to moderate hepatic impairment (total bilirubin ≤ ULN and AST > ULN; or total bilirubin ≤ 3× ULN). The effect of eGFR < 30 mL/min/1.73 m² or dialysis, or 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to assess carcinogenic risk of lumasiran have 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

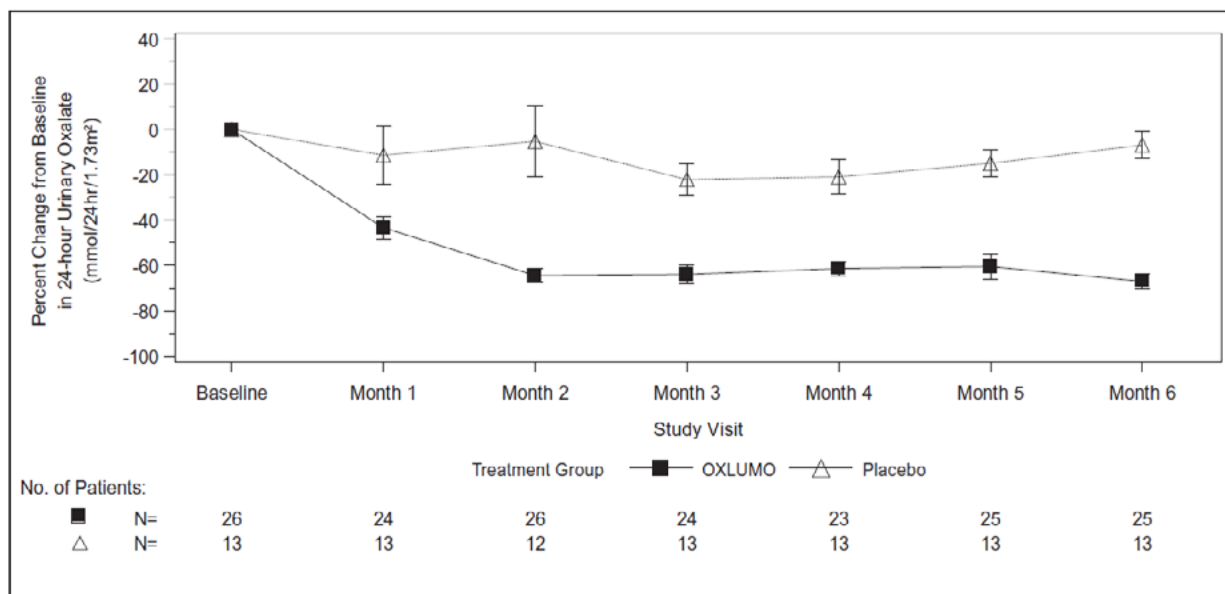
14.1 ILLUMINATE-A

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 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)].

The median age 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



Abbreviations: SEM = standard error of mean.

Results are plotted as mean (\pm SEM) 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).

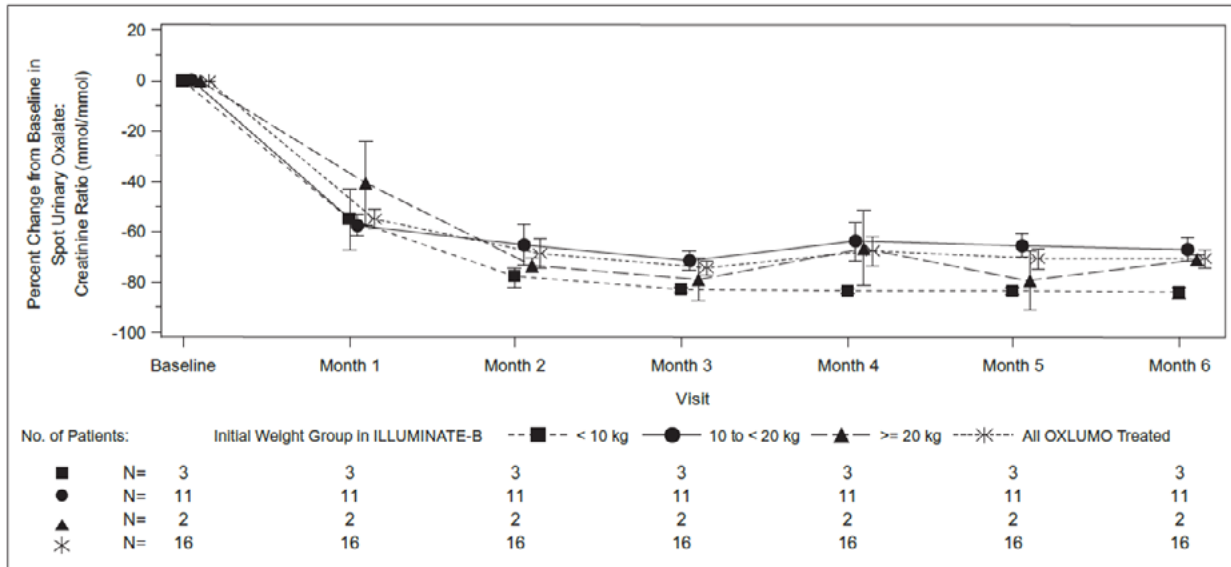
14.2 ILLUMINATE-B

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). Efficacy analyses included the first 16 patients who received 6 months of treatment with OXLUMO. Dosing was based on body weight [see *Dosage and Administration* (2.1)].

The median age was 47 months (range 4 to 74 months), 56% were female, and 88% were White. Three patients were less than 10 kg, 11 were 10 kg to < 20 kg, and 2 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 71% (95% CI: 65, 77) [Figure 2].

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



Abbreviations: SEM = standard error of mean.
 Results are plotted as mean (\pm SEM) of percent change from baseline.

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

Manufactured by: Vetter Pharma-Fertigung GmbH & Co. KG, Eisenbahnstrasse 2-4, 88085 Langenargen, Germany