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RESEARCH**

APPLICATION NUMBER:

214103Orig1s000

LABELING

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 $\geq 20\%$ 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)*].

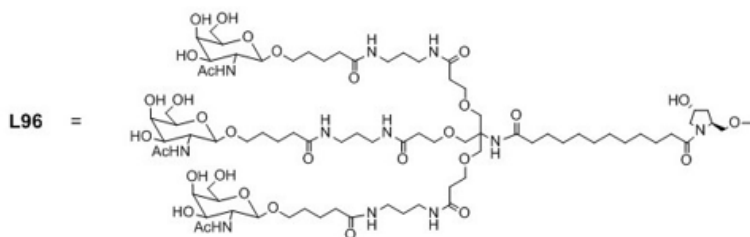
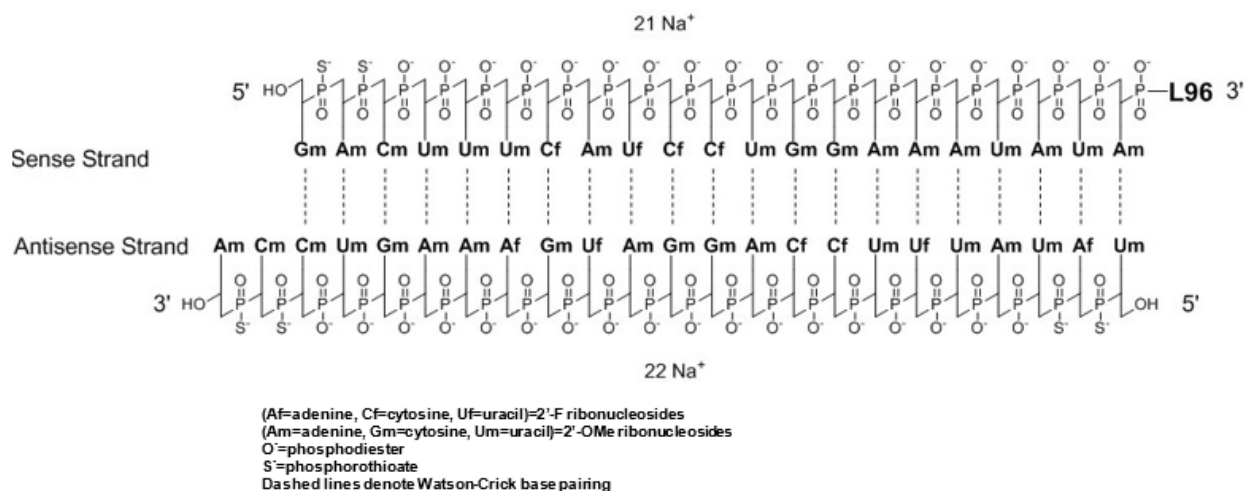
8.7 Renal Impairment

No dose adjustment is necessary in patients with an estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73 m² [see *Clinical Pharmacology (12.3), Clinical Studies (14)*]. OXLUMO has not been studied in patients with an eGFR < 30 mL/min/1.73 m² or patients on dialysis [see *Clinical Pharmacology (12.3)*].

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 C₅₃₀H₆₆₉F₁₀N₁₇₃O₃₂₀P₄₃S₆Na₄₃ 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-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 ≤ 3x 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

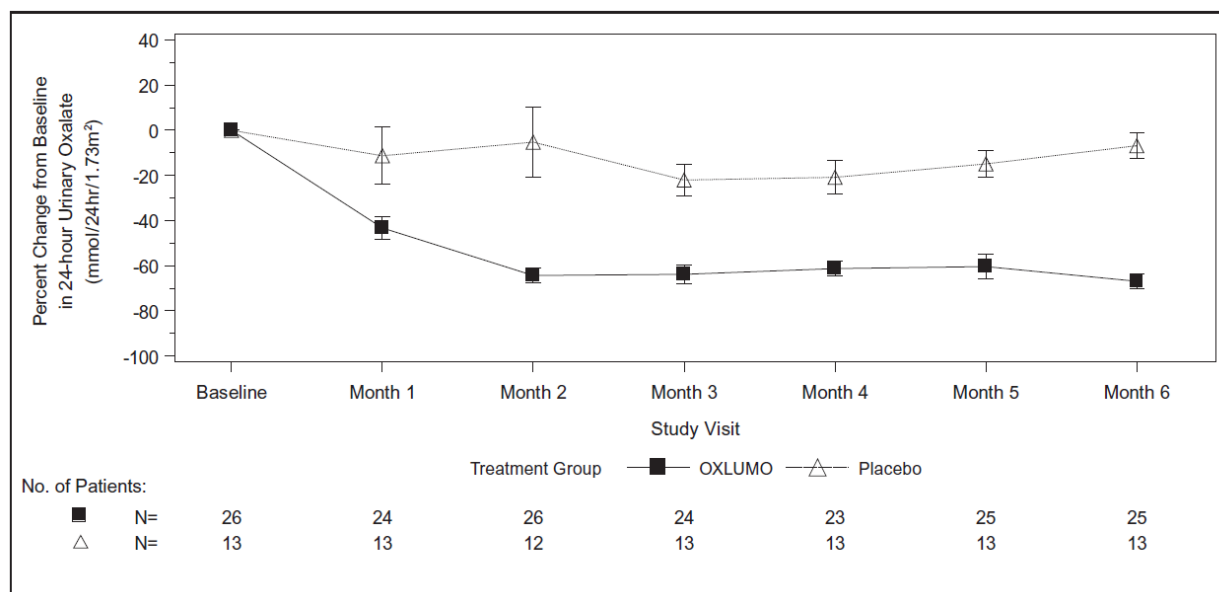
14.1 ILLUMINATE-A

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 ($p=0.001$).

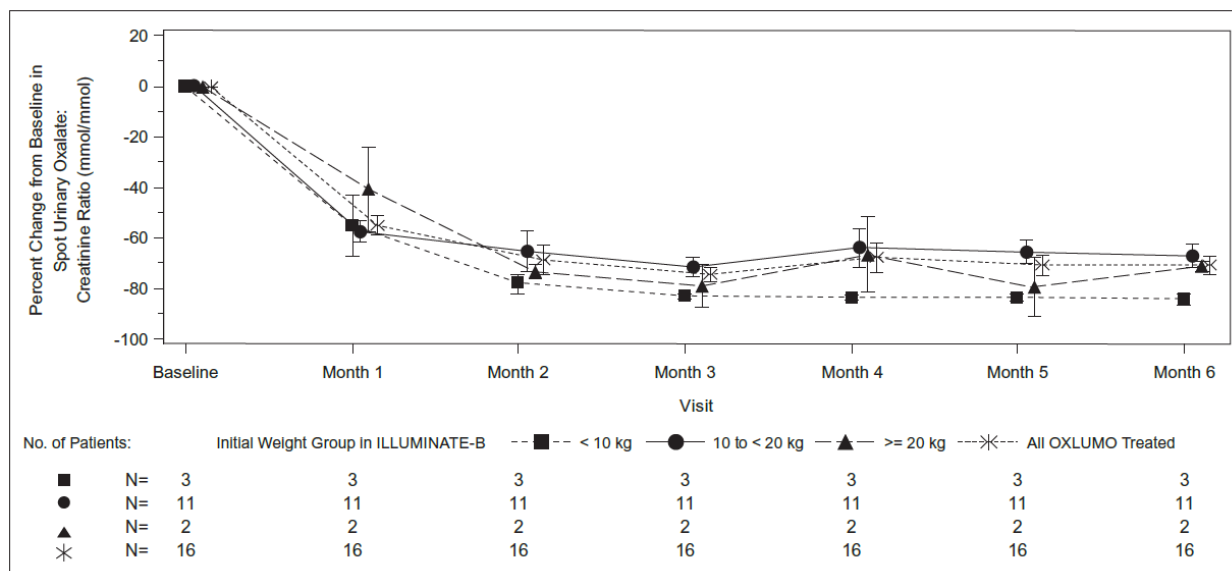
14.2 ILLUMINATE-B

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).

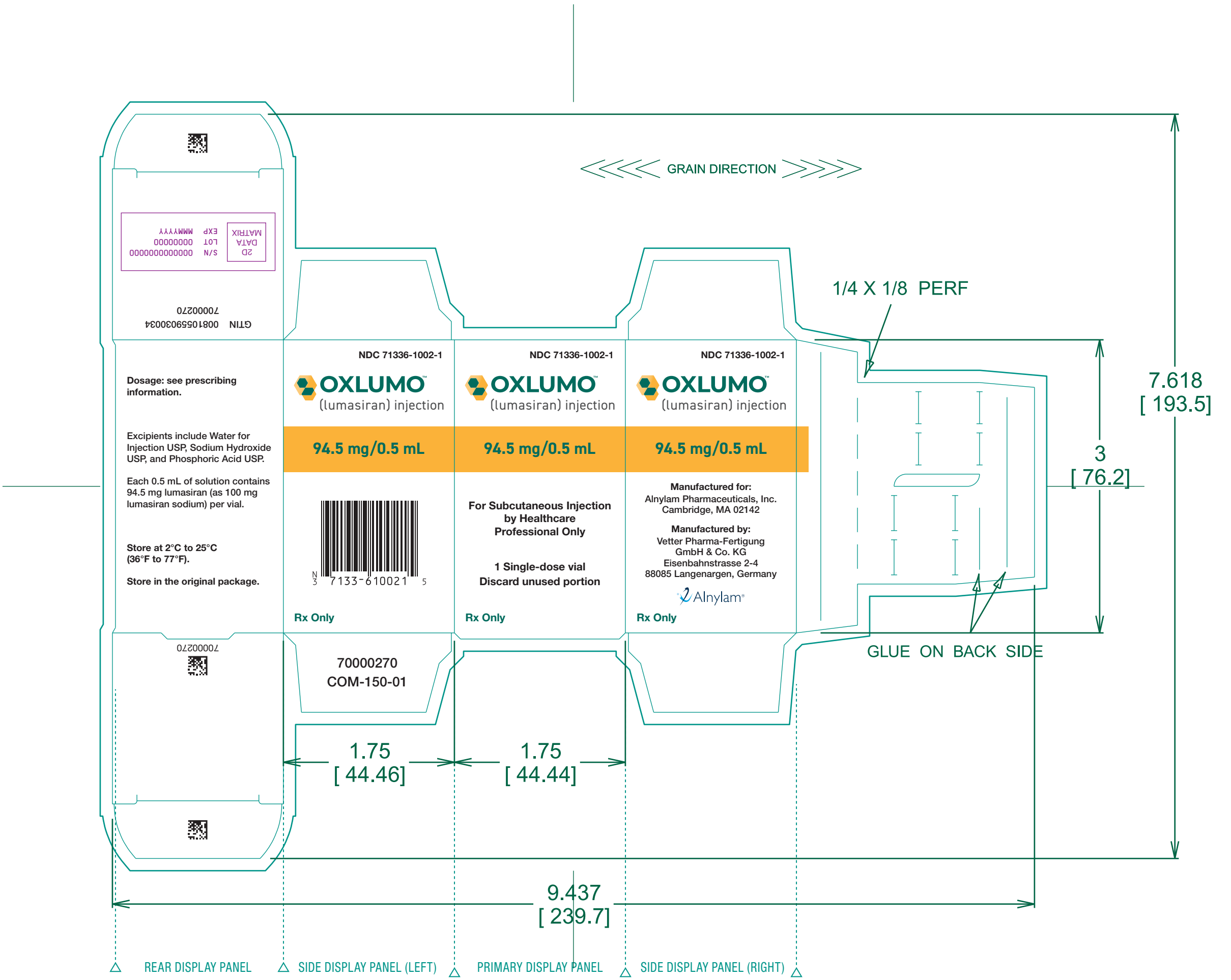
16.2 Storage and Handling

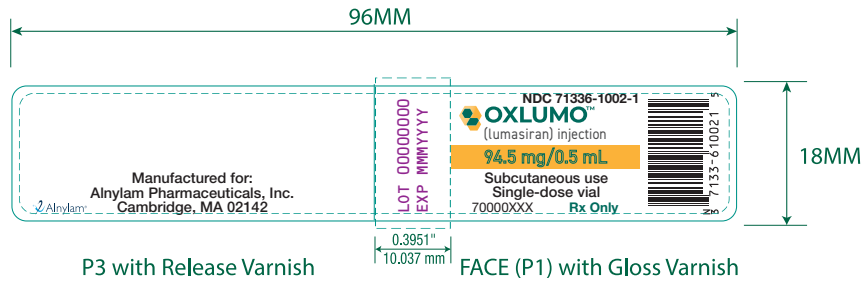
Store at 2°C to 25°C [36°F to 77°F].

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





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/s/

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