Lumasiran: Pregnancy and Lactation

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The full Prescribing Information for OXLUMO® (lumasiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

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SUMMARY

- In lumasiran preclinical studies, there was no impact on fertility endpoints observed in male or female rats.[1]
- In the Phase 2 and ILLUMINATE studies, pregnant or breastfeeding women were excluded from participation. Females of childbearing potential were required to initiate an effective birth control method. Therefore, no data on the safety of lumasiran are available in this population.[2–5]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risk associated with exposure to lumasiran during pregnancy.[6]

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PRECLINICAL DATA

Placental Transfer

Placental, fetal liver, and fetal tissue concentrations of lumasiran were measured concomitantly with studies on embryo-fetal development in rats and rabbits. Lumasiran was not detected in fetal tissue and liver samples. No lumasiran was detected in the placenta of the low dose group (3 mg/kg) and only in low concentrations in the higher dose groups (10 mg/kg and 30 mg/kg) of both species.[7]

CLINICAL DATA

Phase 2 OLE

The Phase 2 OLE study was a multicenter, open-label, extension study to evaluate the long-term safety and tolerability of lumasiran in patients with PH1. Patients with PH1 who completed the Phase 1/2 parent study (NCT02706886) were eligible to enroll in the Phase 2 OLE study.[8]

Pregnant or lactating women were excluded from participation, and females of childbearing potential were required to initiate an effective birth control method.[2]

The need for contraception and compliance with contraception requirements was assessed at every visit for adolescent patients, and pregnancy testing was performed before every dose for women of childbearing potential throughout the study. For any women with a positive pregnancy test during the study, the study drug was discontinued but the patient was followed for safety outcomes.[2]

ILLUMINATE-A

ILLUMINATE-A was a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of lumasiran in adults and children ≥6 years old with PH1 and an eGFR ≥30 mL/min/1.73m^2. Patients were randomized (2:1) to receive subcutaneous injections of lumasiran 3 mg/kg (N=26) or placebo (N=13) once monthly for 3 loading doses, followed by maintenance doses once every 3 months beginning 1 month after the last loading dose. The primary endpoint was the percent change from baseline in 24-hour UOx excretion corrected for BSA at 6 months (average of visits from month 3 through 6). After the 6-month double-blind treatment period, patients continuing in an optional 54-month OLE received lumasiran.[9]

The ILLUMINATE-A protocol addressed pregnant or lactating women, females of childbearing potential, assessments for the need for contraception and compliance with contraception requirements, and pregnancy testing similarly to that of the Phase 2 OLE study.[3]

ILLUMINATE-B

ILLUMINATE-B (N=18) was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by a 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children <6 years old with PH1 and an eGFR >45 mL/min/1.73m^2 (or normal serum creatinine for infants <12 months old). Patients received subcutaneous injections of lumasiran as determined by a body weight-based dosing regimen. The primary endpoint was the percent change from baseline in spot UOx:Cr at 6 months.[10]

The ILLUMINATE-B protocol addressed pregnant or lactating women, females of childbearing potential, assessments for the need for contraception and compliance with contraception requirements, and pregnancy testing similarly to that of the Phase 2 OLE study.[4]

ILLUMINATE-C

ILLUMINATE-C was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in full term infants to adult patients with PH1 and advanced kidney disease with an eGFR ≤45 mL/min/1.73m^2 (or elevated serum creatinine if <12 months old) and POx ≥20 µmol/L. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15). Patients received subcutaneous injections of lumasiran as determined by a body weight-based dosing regimen. The primary endpoints were the percent change from baseline in POx at 6 months (Cohort A) and percent change from baseline in predialysis POx at 6 months (Cohort B).[11]

The ILLUMINATE-C protocol addressed pregnant or lactating women, females of childbearing potential, assessments for the need for contraception and compliance with contraception requirements, and pregnancy testing similarly to that of the Phase 2 OLE study.[5]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risk associated with exposure to lumasiran during pregnancy. The use of lumasiran in pregnant or lactating women and effects on pregnancy outcomes remains missing information and will be closely monitored through routine and additional pharmacovigilance activities.[6]

OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[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.

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.

ABBREVIATIONS

BSA = body surface area; eGFR = estimated glomerular filtration rate; MRHD = recommended human dose; OLE = open-label extension; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; UOx = urinary oxalate; UOx:Cr = urinary oxalate to creatinine ratio.

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