Givosiran: Pregnancy and Lactation

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SUMMARY

- No formal clinical studies of the use of givosiran in pregnant or lactating women have been performed.[1]
- Pregnant or lactating women were excluded from givosiran clinical trials. Women of childbearing potential enrolled in the clinical trials were required to use acceptable methods of birth control.[2,3]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns with the use of givosiran in pregnant or lactating patients.[4]

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[1]:

Pregnancy

Risk Summary

In animal reproduction studies, subcutaneous administration of givosiran to pregnant rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses that produced maternal toxicity.

There are no available data with GIVLAARI use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider the benefits and risks of GIVLAARI for the mother and potential adverse effects to the fetus when prescribing GIVLAARI to a pregnant woman.

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.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Porphyria attacks during pregnancy, often triggered by hormonal changes, occur in 24% to 95% of AHP patients, with maternal mortality ranging from 2% to 42%. Pregnancy in AHP patients is associated with higher rates of spontaneous abortion, hypertension and low birth weight infants.

Data

Animal Data

In an embryo-fetal development study in pregnant rabbits, givosiran was administered subcutaneously at doses of 0.5, 1.5, and 5 mg/kg/day during organogenesis (gestational days 7-19) or 20 mg/kg as a single administration on gestation day 7. Administration of givosiran was maternally toxic based on decreased body weight gain at all dose levels tested and resulted in increased postimplantation loss starting at 1.5 mg/kg/day. An increased incidence of skeletal variations of the sternebrae was observed at 20 mg/kg. The 1.5 mg/kg/day dose in rabbits is 5 times the maximum recommended human dose (MRHD) of 2.5 mg/kg/month normalized to 0.089 mg/kg/day, based on body surface area. In a combined fertility and embryo-fetal development study in female rats, givosiran was administered subcutaneously at doses of 0.5 to 5 mg/kg/day during organogenesis (gestational days 6-17). The 5 mg/kg/day dose (9 times the normalized MRHD based on body surface area) was associated with a skeletal variation (incomplete ossification of pubes) and produced maternal toxicity.

In a pre- and postnatal development study, givosiran administered subcutaneously to pregnant rats on gestation days 7, 13, and 19 and postnatal days 6, 12, and 18 at doses up to 30 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

Lactation

Risk Summary

There are no data on the presence of GIVLAARI in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GIVLAARI and any potential adverse effects on the breastfed child from GIVLAARI or from the underlying maternal condition.

NONCLINICAL DATA

In nonclinical studies, givosiran had no adverse effects on male or female fertility, pregnancy, or embryo-fetal development at doses that did not result in maternal toxicity.[4] There is no suspicion of human teratogenicity based on class effects or genotoxic potential. Givosiran was neither genotoxic nor clastogenic in *in vitro* and *in vivo* studies.[3]

CLINICAL DATA

Phase 1 Study

The Phase 1 study was a multicenter, randomized, placebo-controlled, 3-part study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran in patients with AIP.[5]

In Part B of the study, a SAE of spontaneous abortion occurred in a patient with AIP at 7 weeks after conception and 90 days after the last givosiran dose of 1.0 mg/kg.[5] The patient received a total of two doses of givosiran 1.0 mg/kg, 1 month apart, and had a previous history of spontaneous abortion. Per protocol, the use of highly effective contraception was stipulated until the end of study visit (42 days after receiving the last dose of study drug); therefore, conception likely occurred around the 42-day limit. At the time of spontaneous abortion, the patient's ALA and PBG levels had not returned to the patient's baseline values but were close to levels found in normal healthy individuals.[6]

Investigators were unable to determine whether this event was independent of treatment because the rate of such events is approximately 20% of all pregnancies, and some studies suggest that the frequency of spontaneous abortion may be higher among patients with AIP than among healthy women. Preclinical biodistribution studies have shown that givosiran is predominantly distributed to the liver, with exposure levels in extrahepatic tissues so low that they would not be expected to result in pharmacodynamic activity.[5]

ENVISION Study

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (N=48) or placebo (N=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.[7]

Inclusion Criteria

Patients had to meet all inclusion criteria to be eligible for enrollment in the study, including the following[3]:

- Was willing to comply with the contraceptive requirements during the study period

Women of child-bearing potential must have been willing to use acceptable methods of contraception from 14 days before the first dose and throughout study participation, including the 6-month double-blind treatment period and extension period through the End of Study visit or Safety Follow-up visit, if the patient discontinued the study prior to its completion.[3]

Exclusion Criteria

Patients were excluded from the study if the following criteria applied[3]:

- Females who were pregnant, breast-feeding, or planning to become pregnant during the study

Protocol

Female patients of childbearing potential were required to have a negative pregnancy test result at the study visits. Patients who became pregnant were discontinued from givosiran immediately, with a positive urine pregnancy test confirmed by a serum pregnancy test prior to discontinuing givosiran. If a patient became pregnant during the course of the study through 3 months following the last dose of givosiran, the Investigator was required to report the pregnancy within 24 hours of being notified of the pregnancy. The patient was to receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring of the patient was to continue until the conclusion of the pregnancy, and the outcome of the pregnancy was to be reported.[3,8]

Pregnancies

Three patients became pregnant while being treated with givosiran. These cases are presented below[8]:

- One patient became pregnant and withdrew from the study after her third monthly dose of givosiran. The patient terminated the pregnancy and underwent an induced abortion.
- One patient discontinued givosiran treatment and withdrew from the study due to pregnancy after her 30th monthly dose of givosiran. The patient chose to terminate the pregnancy, and an elective abortion occurred.
- One patient discontinued givosiran treatment when she planned to become pregnant and received her last (28th) dose of givosiran on Day 813. The patient's pregnancy began on Day 866. She experienced a SAE of spontaneous abortion on Day 948 that was mild in intensity and was considered not related to givosiran by the Investigator. The patient withdrew from the study on Day 1025.

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns with the use of givosiran in pregnant or lactating patients based on the available data. The risk of givosiran to pregnancy outcomes and to the fetus and infant remains unknown. The benefit-risk balance of givosiran therapy during pregnancy should be considered.[4]

ABBREVIATIONS

AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALA = δ-aminolevulinic acid; OLE = open-label extension; PBG = porphobilinogen; SAE = serious adverse event.

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