Vutrisiran: Pregnancy & Lactation

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SUMMARY

- Vutrisiran has undergone comprehensive toxicology testing, demonstrating no genotoxic or clastogenic effects. Animal studies showed no evidence of direct embryofetal toxicity, detectable level of vutrisiran in the fetus at any dose, or development effects from exposure during lactation.[1]
- In the HELIOS-A and HELIOS-B studies, pregnant or breastfeeding women were excluded from participation. Women of childbearing potential were required to provide a negative pregnancy test, confirm they were not breastfeeding, and use highly effective contraception. Therefore, no data on the safety of vutrisiran are available in this population.[2,3]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risks associated with exposure to vutrisiran during pregnancy.[1]

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PRECLINICAL DATA

A comprehensive program of toxicology studies has been performed with vutrisiran, which includes single-dose toxicity, repeat-dose toxicity, genotoxicity, and reproductive toxicity.[4]

Genotoxicity

Vutrisiran was not mutagenic in Ames test and a mammalian cell assay in human lymphocytes with and without metabolic activation in vitro. In studies of rats, vutrisiran did not induce micronuclei in the bone marrow, and no toxicity was observed at the highest vutrisiran dose.[4]

Reproductive Toxicity

The reproductive and developmental toxicity of subcutaneous administration of vutrisiran was examined in studies of fertility and early embryonic development in rats, embryofetal development in rats and rabbits, and on prenatal and postnatal development in rats. In pregnant rats and rabbits, vutrisiran was detected in placenta. However, in the fetal liver or the remainder of fetal carcasses of both species, vutrisiran levels were below the level of quantification, indicating that vutrisiran was not transferred to the fetus.[4]

Fertility and Embryofetal Development

In the pivotal fertility and early embryonic development study, vutrisiran did not impact early embryonic development with a NOAEL of 70 mg/kg/week (323-fold the MRHD normalized to 0.035 mg/kg/week).[4]

In the vutrisiran dose-range finding study on fertility and development in rats, a single dose of the rodent-specific vutrisiran orthologue resulted in anticipated reductions of thyroxine and vitamin A. Vutrisiran was quantifiable in the maternal placenta but was not found in the fetal livers or other fetal tissues.[4]

In the embryofetal development study in rats, administration of vutrisiran resulted in maternal toxicity, such as macroscopic and microscopic findings in different organs (liver, pancreas, and uterus) and adverse effects on body weight gain and food consumption. During Caesarean and fetal evaluations, increased premature delivery, increased post-implantation loss, decrease in viable fetus, and a reduction in fetal body weights were reported. At high doses, an increased incidence of skeletal variations was observed in fetuses, but with no gross external or visceral anomalies. The NOAEL was established at 10 mg/kg/day for maternal toxicity and at 3 mg/kg/day for embryofetal development.[4]

In the embryofetal development study in rabbits, vutrisiran had no effect on maternal parameters or embryofetal development, of which the NOAEL for maternal toxicity and embryofetal development was 30 mg/kg/day. Vutrisiran was quantifiable in maternal liver and kidney of pregnant rabbits, whereas low concentrations were found in the placenta. In all fetal tissue, vutrisiran was below the level of quantification indicating that maternal exposure did not result in the transfer of vutrisiran to fetuses.[4]

Prenatal and Postnatal Development, Including Maternal Function

In the prenatal and postnatal development study in rats, vutrisiran administered every sixth day had no observed effect on the dams as well as on growth and development of offspring, with the NOAEL for the F0 and F1 generation established at 20 mg/kg. Vutrisiran was not detected in plasma samples of F1 offspring exposed to vutrisiran via milk. However, the milk transfer of vutrisiran cannot be entirely excluded due to the time gap between maternal vutrisiran administration and plasma sampling in the offspring.[4]

CLINICAL DATA

HELIOS-A Study

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[5]

Pregnant or breastfeeding women were excluded from participating in the clinical study. Women of child-bearing potential were required to provide a negative pregnancy test, not be breastfeeding, and utilize a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after the last administration of the study drug.[2]

HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind treatment period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[6]

Women who were pregnant, breastfeeding, or planning a pregnancy were excluded from participating in the clinical study. Women of child-bearing potential were required to provide a negative pregnancy test, not be breastfeeding, and utilize a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after the last administration of the study drug.[3]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risks associated with exposure to vutrisiran during pregnancy. The use of vutrisiran in pregnant or lactating women and effects on pregnancy outcomes remains missing information and will be closely monitored through routine and additional pharmacovigilance activities.[1]

AMVUTTRA US PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[7]:

Pregnancy

Risk Summary

There are no available data on AMVUTTRA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. AMVUTTRA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking AMVUTTRA. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by AMVUTTRA and of vitamin A supplementation are unknown.

In animal studies, subcutaneous administration of vutrisiran to pregnant rats resulted in developmental toxicity (reduced fetal body weight and embryofetal mortality) at doses associated with maternal toxicity.

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. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rats during the period of organogenesis resulted in embryofetal mortality at the high dose and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rabbits resulted in no adverse effects on embryofetal development.

Subcutaneous administration of vutrisiran (0, 5, 10, or 20 mg/kg) to pregnant rats every 6 days throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation

Risk Summary

There is no information regarding the presence of vutrisiran in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMVUTTRA and any potential adverse effects on the breastfed infant from AMVUTTRA or from the underlying maternal condition.

The PATIENT COUNSELING INFORMATION section provides the following information[7]:

Instruct patients that if they are pregnant or plan to become pregnant while taking AMVUTTRA they should inform their healthcare provider. Inform patients of the potential risk to the fetus, including that AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

ABBREVIATIONS

ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; GD = gestational day; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; MRHD = maximum recommended human dose; NOAEL = no observed adverse effect level; OLE = open-label extension; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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