Vutrisiran: Use in Patients with Hepatic Impairment

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SUMMARY

- In the HELIOS-A and HELIOS-B trials, patients were excluded if they[1–3]:
  - had or were likely to undergo liver transplantation
  - had AST and/or ALT >1.5x and 2x the ULN, total bilirubin >ULN and 2x the ULN, or INR >1.2 and 1.5.
  - A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns pertaining to the use of vutrisiran in patients with moderate or severe hepatic impairment. Use in patients with moderate and severe hepatic impairment is closely monitored through routine pharmacovigilance activities.[4]

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AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The **USE IN SPECIFIC POPULATIONS** section provides the following information[5]:

Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) or moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. AMVUTTRA has not been studied in patients with severe hepatic impairment.

The **CLINICAL PHARMACOLOGY** section provides the following information[5]:

Pharmacokinetics: Specific Populations

No clinically significant differences in the pharmacokinetics of vutrisiran were observed based on age, sex, race, mild and moderate renal impairment (eGFR≥30 to <90 mL/min/1.73 m^2), or mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, severe hepatic impairment, or in patients with prior liver transplant.

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.[1]

Per the HELIOS-A study protocol, patients were excluded from the study if they[1,2]:

- Had a liver transplant or were likely to undergo liver transplantation during the 18-month treatment period.
- Had any of the following laboratory parameter assessments:
  - ALT and/or AST >1.5x ULN
  - Total bilirubin >ULN (>1.5x ULN in patients with Gilbert's Syndrome)
  - INR >1.2 (Patients on anticoagulant therapy with an INR of ≤3.5 were allowed)
  - Note: ALT, AST, and total bilirubin laboratory criteria had to be met at both Screening Visit 1 and Screening Visit 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 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]

Per the HELIOS-B study protocol, patients were excluded from the study if they[3]:

- Had prior or anticipated (during the first 12 months after randomization) liver transplant.
- Had any of the following laboratory parameter assessments:
  - AST or ALT >2.0x ULN
  - Total bilirubin >2.0x ULN
  - INR >1.5 (Patients on anticoagulant therapy were excluded if INR >3.5)

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns pertaining to the use of vutrisiran in patients with moderate or severe hepatic impairment. Use in patients with moderate and severe hepatic impairment is closely monitored through routine pharmacovigilance activities.[4]

ABBREVIATIONS

ALT = alanine transaminase; AST = aspartate transaminase; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; INR = international normalized ratio; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; ULN = upper limit of normal; wtATTR = wild-type transthyretin amyloidosis.

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REFERENCES

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