Vutrisiran: Use in Patients with Renal Impairment

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CLINICAL PHARMACOLOGY INFORMATION

Vutrisiran targets the liver and is not primarily directed at the kidney. As renal excretion is a minor route of elimination for vutrisiran, severe renal impairment or ESRD is not anticipated to significantly affect overall PK parameters.[1]

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 the polyneuropathy of hATTR. 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 (NCT01960348) 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 the mNIS+7 at 9 months.[2]

Select Inclusion and Exclusion Criteria

Patients with adequate renal function were included in the study.[2] Patients with eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) were excluded from the study.[3]

No additional information is currently available regarding the use of vutrisiran in patients with renal impairment in the HELIOS-A study.

HELIOS-B Study

HELIOS-B (NCT04153149) was a Phase 3, global, randomized, double-blind, placebo-controlled multicenter study designed to evaluate the efficacy and safety of vutrisiran compared to placebo in patients with ATTR with cardiomyopathy, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg or placebo 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 exposure period in the overall population and in the vutrisiran monotherapy subgroup.[4]

Select Inclusion and Exclusion Criteria

Patients with eGFR <30 mL/min/1.73 m^2 (using the MDRD formula) were excluded from the study.[5]

No additional information is currently available regarding the efficacy or safety of vutrisiran in the HELIOS-B study.

GLOBAL SAFETY DATABASE

Renal Impairment

A cumulative postmarketing review of the vutrisiran global safety database did not identify any new safety concerns with vutrisiran use in patients with a history of severe renal impairment or ESRD.[6]

The available data from the global safety database do not suggest an increased risk or varying safety profile with use of vutrisiran in patients with severe renal impairment or ESRD.

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

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

Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73 m^2). AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

The CLINICAL PHARMACOLOGY section provides the following information[7]:

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 hepatic impairment (total bilirubin ≤1 × ULN and AST >1 × ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST). Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, moderate or severe hepatic impairment, or in patients with prior liver transplant.

ABBREVIATIONS

AST = aspartate aminotransferase; ATTR = transthyretin-mediated amyloidosis; CV = cardiovascular; ESRD = end-stage renal disease; hATTR = hereditary transthyretin-mediated amyloidosis; IV = intravenous; MDRD = Modification of Diet in Renal Disease; mNIS+7 = modified Neuropathy Impairment Score +7; PK = pharmacokinetic; ULN = upper limit of normal; wtATTR = wild-type transthyretin-mediated amyloidosis.

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