Vutrisiran: Use in Patients with Renal Impairment

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SUMMARY

- Patients with an eGFR <30 mL/min/1.73 m^2 were excluded from the phase 3 HELIOS-A and HELIOS-B trials; therefore, the use of vutrisiran in patients with severe renal impairment or ESRD have not been evaluated in clinical studies.[1,2]
- Clinical pharmacology studies have demonstrated that renal excretion is a minor route of elimination for vutrisiran.[3]
- Severe renal impairment or ESRD is not anticipated to significantly influence the overall systemic exposure, liver uptake, pharmacodynamics, or safety of vutrisiran.[4]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns with the use of vutrisiran in patients with a history of severe renal impairment or ESRD. The available data from the global safety database do not suggest an increased risk or varying safety profile with the use of vutrisiran in this population.[4,5]

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AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[6]:

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[6]:

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

Phase 1 Study

A phase 1, randomized, single-blind, placebo-controlled, single ascending dose study was conducted to evaluate the safety, tolerability, PK, and PD of a single dose of vutrisiran in healthy subjects. The subjects were scheduled to receive a single dose of either subcutaneous vutrisiran (n=60) or placebo (n=20). Study subjects were enrolled in cohorts to receive 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg of vutrisiran.[3]

Pharmacokinetic Data

Evaluable PK data were available from all 60 subjects who received vutrisiran. The mean serum $t_{1/2}$ ranged from 4.2 to 7.5 hours following subcutaneous administration of vutrisiran. After reaching the C_{max}, 40% and 98% of vutrisiran concentrations declined to the LLOQ by 24 to 48 hours, respectively, due to the rapid ASGPR-facilitated liver uptake of vutrisiran from systemic circulation. Across the dose levels tested, the mean renal clearance ranged from 4.45 to 5.74 L/h. The fraction of renal clearance to total clearance ranged from 15.5 to 27.5%, indicating that renal excretion is a minor route of elimination of vutrisiran.[3]

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.[3,7]

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 the mNIS+7 at 9 months.[8]

Select Exclusion Criteria

Patients with adequate renal function were included in the study.[8] Per the HELIOS-A study protocol, patients with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) were excluded.[1]

Pharmacokinetic Data

After reaching the C_{max}, plasma concentrations of vutrisiran declined to the LLOQ by 24 hours in a majority of patients in the HELIOS-A study. At the dose regimen of 25 mg every 3 months, the population estimate of mean serum $t_{1/2}$ was 6.29 hours and the mean apparent total body clearance was 21.6 L/h. For a 70 kg patient with normal renal function, the model-estimated renal clearance was 5.4 L/h.[7]

Pooled Safety Population

In a pooled PK/PD population (n=202) including data from the Phase 1 and HELIOS-A studies, patients with mild to moderate renal impairment showed similar TTR reductions similar to those with no renal impairment. No significant impact of impaired renal function was observed, with a less than 25%

increase in C_{max} and AUC_{0-24} predicted in patients with mild or moderate renal impairment compared with patients with normal renal function.[7]

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.[9]

Select Exclusion Criteria

Per the HELIOS-B study protocol, patients with an eGFR <30 mL/min/1.73 m^2 (using the MDRD formula) were excluded from the study.[10]

No additional information is currently available regarding the efficacy or safety of vutrisiran in patients with severe renal impairment or ESRD.

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns with the use of vutrisiran in patients with a history of severe renal impairment or ESRD. The available data from the global safety database do not suggest an increased risk or varying safety profile with use of vutrisiran in this population.[4,5]

ABBREVIATIONS

ASGPR = asialoglycoprotein receptor; AST = aspartate aminotransferase; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; AUC_{0-24} = area under the concentration time curve from 0 to 24 hours; C_{max} = maximum serum concentration; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; hATTR = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; LLOQ = lower limit of quantification; MDRD = Modification of Diet in Renal Disease; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; TTR = transthyretin; ULN = upper limit of normal; wtATTR = wild-type transthyretin-mediated amyloidosis.

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