Patisiran: Use in Patients Undergoing Dialysis

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The full Prescribing Information for ONPATTRO® (patisiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

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SUMMARY

- Patisiran has not been studied in patients with severe renal impairment or ESRD, or in patients undergoing any type of dialysis; therefore, the risk of its use in this patient population is unknown.[1]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any specific pattern or concern involving patients with severe renal impairment or ESRD.[2]

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CLINICAL DATA

Drug Product Information

The drug product is a homogenous solution of nucleic acid/lipid nanoparticles with an average size of approximately 60–100 nm. The molecular weight is 14,304 Da.[3]

Clinical Pharmacology Information

Across various clinical pharmacology studies including both healthy subjects and patients with hATTR-PN, after IV infusion of patisiran, the C_{max} was reached at approximately the end of infusion, followed by a rapid decline due to distribution and active uptake of the LNPs from the plasma by the liver. The apparent distribution phase half-life, $t_{1/2\alpha}$, was approximately 0.282 to 2.32 hours across various studies.[4] Clinical pharmacology data have shown that urinary excretion is a minor clearance pathway for the siRNA and the lipid DLin-MC3-DMA components of patisiran.[2]

Pooled Safety Population

In a pooled safety population (N=224) including data from the Phase 2 OLE, APOLLO, and Global OLE (as of January 27, 2021) studies, 48 (21.4%) patients had mild renal impairment, 22 (9.8%) patients had moderate renal impairment, and 1 (0.4%) patient had severe renal impairment at baseline. Patients with severe renal impairment were excluded from clinical trials of patisiran. No increased risk was associated with administration of patisiran to patients with mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73m^2), and no dose adjustments were necessary.[2]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any specific pattern or concern involving patients with severe renal impairment or ESRD. The type of events

noted within this patient population were generally consistent with that expected for the condition being treated and the known safety profile of patisiran.[2]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

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

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

The CLINICAL PHARMACOLOGY section provides the following information[1]:

Pharmacokinetics

Following a single intravenous administration, systemic exposure to patisiran increases in a linear and dose proportional manner over the range of 0.01 to 0.5 mg/kg. Greater than 95% of patisiran in the circulation is associated with the lipid complex. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, steady state is reached by 24 weeks of treatment. The estimated mean ± SD steady state peak concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_t) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_t was 3.2-fold at steady state, compared to the first dose. In the placebo-controlled study, inter-patient variability in patisiran exposure did not result in differences in clinical efficacy (mNIS+7 change from baseline) or safety (adverse events, serious adverse events).

Distribution

Plasma protein binding of ONPATTRO is low, with ≤2.1% binding observed in vitro with human serum albumin and human α1-acid glycoprotein. ONPATTRO distributes primarily to the liver. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, the mean ± SD steady state volume of distribution of patisiran (V_{ss}) was 0.26 ± 0.20 L/kg.

Elimination

The terminal elimination half life (mean ± SD) of patisiran is 3.2 ± 1.8 days. Patisiran is mainly cleared through metabolism, and the total body clearance (mean ± SD) at steady state (CL_{ss}) is 3.0 ± 2.5 mL/h/kg.

Excretion

Less than 1% of the administered dose of patisiran is excreted unchanged into the urine.

Specific Populations

Age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of patisiran or TTR reduction. Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73 m^2) or mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN) on patisiran exposure or TTR reduction. ONPATTRO has not been studied in patients with severe renal impairment, end-stage renal disease, or moderate or severe hepatic impairment.

ABBREVIATIONS

AST = aspartate aminotransferase; AUC_t = area under the curve; CL_{ss} = steady state clearance; C_{max} = peak concentration; C_{trough} = trough concentration; Da = dalton; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; LNP = lipid nanoparticle; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; SD = standard deviation; siRNA = small interfering RNA; $t_{1/2a}$ = apparent distribution phase half-life; TTR = transthyretin; ULN = upper limit of normal; V_{ss} = steady state volume of distribution.

REFERENCES

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4. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2100042.