Vutrisiran: Use in Patients Undergoing Dialysis

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SUMMARY

- Patients with severe renal impairment or ESRD were excluded from vutrisiran clinical studies; therefore, the use of vutrisiran in patients undergoing dialysis is unknown.[1,2]
- 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 severe renal impairment or ESRD.[3]

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CLINICAL DATA

Clinical Pharmacology Information

Across various clinical pharmacology studies including both healthy subjects and patients with hATTR-PN, the mean serum $t_{1/2}$ ranged from 4 to 7.5 hours following subcutaneous administration of vutrisiran. After reaching the C_{max}, vutrisiran concentration declined rapidly to the LLOQ by 24 to 48 hours. Clinical pharmacology data have shown that renal clearance is not a major route of elimination of vutrisiran.[4]

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 compared 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 to patients with normal renal function.[4]

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 severe renal impairment or ESRD.[3]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

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

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[5]:

Pharmacokinetics

The pharmacokinetic (PK) properties of AMVUTTRA were evaluated following a single dose in healthy subjects and multiple doses in patients with hATTR amyloidosis, as summarized in ***Table 2****.*

Table 2: Pharmacokinetic Parameters of Vutrisiran

	Vutrisiran
General Information	
Dose Proportionality	*Vutrisiran C_{max} showed dose proportional increase while AUC_{last} and AUC_{inf} were slightly more than dose proportional following single subcutaneous doses ranging from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose)*
Accumulation	*No accumulation of vutrisiran was observed in plasma after repeated every 3 months dosage[a]*
Absorption	
T_{max} [Median (Range)]	*4 (0.17, 12.0) hours[b]*
Distribution	
Estimated Vd/F (%RSE)	*10.1 (5.8) L[c]*
Protein Binding	*80%[d]*
Organ Distribution	*Vutrisiran distributes primarily to the liver after subcutaneous dosing*
Elimination	
Half-Life [Median (Range)]	*5.2 (2.2, 6.4) hours[b]*
Apparent Clearance [Median (Range)]	*21.4 (19.8, 30) L/hour[b]*
Metabolism	
Primary Pathway	*Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver*
Excretion	
Primary Pathway	*The mean fraction of unchanged vutrisiran eliminated in urine was approximately 19.4% at the recommended dose of 25 mg. The mean renal clearance of vutrisiran ranged from 4.5 to 5.7 L/hour[e]*

AUC_{inf} = area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC_{last} = area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max} = maximum plasma concentration; CV = coefficient of variation; RSE = relative standard error; T_{max} = time to maximum concentration; Vd/F = apparent volume of distribution

[a]After 25 mg every 3 months dosage in hATTR amyloidosis patients

[b]After 25 mg single dose in healthy subjects

[c]Based on population PK model estimation

[d]Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 mcg/mL to 19% at 50 mcg/mL)

[e]After single subcutaneous vutrisiran dose from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose) in healthy subjects

ABBREVIATIONS

AUC_{0-24} = area under the concentration time curve from 0 to 24 hours; AUC_{inf} = area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC_{last} = area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max} = maximum plasma concentration; CV = coefficient of variation; ESRD = end-stage renal disease; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; LLOQ = lower limit of quantification;

PD = pharmacodynamics; PK = pharmacokinetics; RSE = relative standard error; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration; TTR = transthyretin; Vd/F = apparent volume of distribution.

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REFERENCES

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3. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2400036.
4. Amvuttra : EPAR – Public assessment report. European Medicines Agency. Published October 12, 2022. Accessed December 20, 2024. https://www.ema.europa.eu/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf.
5. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.