Givosiran: Use in Patients with Pre-Existing Hepatic Impairment

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CLINICAL DATA

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (N=48) or placebo (N=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.[1]

Key study exclusion criteria were:[2]

- ALT >2×ULN
- Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN.
- On an active liver transplant waiting list, or anticipated to undergo liver transplantation during the blinded study treatment period

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The **CLINICAL PHARMACOLOGY** section provides the following information[3]:

Specific Populations

No clinically meaningful differences in givosiran pharmacokinetics or pharmacodynamics (percent reduction in urinary ALA and PBG) were observed based on age (19 to 65 years), sex, race/ethnicity, mild, moderate or severe renal impairment (eGFR ≥15 to <89 mL/min/1.73m^2 estimated by the Modification of Diet in Renal Disease [MDRD] formula), and mild hepatic impairment (bilirubin ≤1×ULN and AST >1×ULN, or bilirubin >1×ULN to 1.5×ULN).The effect of end-stage renal disease (eGFR <15 mL/min/1.73m^2), and moderate to severe hepatic impairment on givosiran pharmacokinetics is unknown.

ABBREVIATIONS

AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALA = aminolevulinic acid; ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; PBG = porphobilinogen; ULN = upper limit of normal; OLE = open-label extension.

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REFERENCES

1. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol*. 2023;79(5):1150-1158. doi:10.1016/j.jhep.2023.06.013
2. Supplement to: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1807838
3. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.