

Givosiran: Post-Dose Monitoring

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SUMMARY

- The duration of monitoring patients after receiving givosiran is at the clinical discretion of the healthcare provider.
- Per the ENVISION study protocol, patients were observed for a minimum of 20 minutes following each injection.¹

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CLINICAL DATA

ENVISION Study

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.^{2,3}

Per the study protocol, patients were observed for a minimum of 20 minutes following each injection.¹

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The **WARNINGS AND PRECAUTIONS** section provides the following information⁴:

Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

Hepatic Toxicity

Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients treated with GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically meaningful transaminase elevations.

Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of the patients in the GIVLAARI arm experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

Injection Site Reactions

Injection site reactions have been reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. Among 12 patients with reactions, the highest severity of the reaction was mild among 11 (92%) patients and moderate in one (8%) patient. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI. In the ENVISION study, during the open label extension, adverse reactions of blood homocysteine increased were reported in 15 of 93 (16%) patients treated with GIVLAARI. The clinical relevance of the elevations in blood homocysteine during treatment with GIVLAARI is unknown. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

Pancreatitis

Cases of acute pancreatitis, some severe, have been reported in GIVLAARI-treated patients.

Consider acute pancreatitis as a potential diagnosis in GIVLAARI-treated patients with signs/symptoms of acute pancreatitis including acute upper abdominal pain, clinically significant elevation of pancreatic enzymes, and/or imaging findings of acute pancreatitis, to ensure appropriate management. Consider interruption and/or discontinuation of GIVLAARI treatment for severe cases.

ABBREVIATIONS

AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; OLE = open-label extension.

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REFERENCES

1. Protocol for: 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/NEJMoa1913147

2. 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/NEJMoa1913147
3. 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
4. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.