

Givosiran: Pancreatitis

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SUMMARY

- In givosiran clinical studies:
 - One fatal SAE of hemorrhagic pancreatitis was reported in the Phase 1 study in a patient with AIP. The event was considered unlikely to be related to givosiran treatment by the investigator. Following the SAE, no other cases of pancreatitis or clinically significant elevations in lipase were reported.¹
 - In the phase 3 ENVISION OLE, 1 patient discontinued treatment due to an SAE of pancreatitis.²
- A cumulative post-marketing review of Alnylam Pharmaceutical's global safety database did not identify any new safety concerns involving pancreatitis with the use of givosiran.³

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

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

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.

The **ADVERSE REACTIONS** section provides the following information⁴:

Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Acute pancreatitis

CLINICAL DATA

Phase 1 Study

The Phase 1 study was a multicenter, randomized, placebo-controlled, 3-part study (N=23 in Parts A and B; N=17 in Part C) designed to evaluate the safety, tolerability, PK, and PD of givosiran in patients with AIP.¹

One SAE of fatal hemorrhagic pancreatitis was reported in a patient with a complex medical history of obesity, hypertension, bacteremia, and quadriplegia from AIP. The patient experienced clinical complications due to delayed treatment and hospitalization and complications from an acute pulmonary embolism that resulted in right heart failure. The patient was receiving once-monthly injections of givosiran 5 mg/kg. The investigator considered the event unlikely to be related due to the patient's complex history, presence of biliary sludge on ultrasound, and lack of a temporal relationship to givosiran.¹

After the SAE, monthly lipase monitoring was initiated for Part C of the study, in which 14 out of the 17 patients had at least 1 measurement of lipase. No other cases of pancreatitis or lipase elevations greater than three times the upper limit of normal range were observed. There were 2 patients receiving givosiran 5.0 mg/kg quarterly with mild, transient elevations of lipase without clinical features of pancreatitis that spontaneously normalized with continued dosing.^{1,5}

Phase 1/2 OLE Study

The Phase 1/2 OLE study was an extension of the phase 1 study to evaluate the long-term safety and tolerability of givosiran in patients with AIP for up to 48 months. Upon study entry, patients received givosiran 2.5 mg/kg once monthly or 5.0 mg/kg once monthly or every 3 months. All patients enrolled in the OLE (N=16) were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.⁶

A total of 4 patients (25%) had transient increases in lipase levels, with no reported signs or symptoms of pancreatitis. All instances of increased lipase were moderate in severity and resolved during continued treatment with givosiran.⁶

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

During the OLE, increased lipase was reported as an AE in 13 patients (14%). One patient discontinued givosiran treatment due to SAEs of increased blood homocysteine and pancreatitis.²

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceutical's global safety database did not identify any new safety concerns involving pancreatitis with the use of givosiran. Pancreatitis remains an important potential risk and is closely monitored through routine pharmacovigilance activities.³

ABBREVIATIONS

AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; SAE = adverse event.

Updated 26 February 2026

REFERENCES

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3. Alnylam Pharmaceuticals. Data on file. MED-ALL-GIVO-2500004.
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6. Sardh E, Balwani M, Rees DC, et al. Long-term follow-up of givosiran treatment in patients with acute intermittent porphyria from a phase 1/2, 48-month open-label extension study. *Orphanet J Rare Dis*. 2024;19(1). doi:10.1186/s13023-024-03284-w