Givosiran: Pancreatitis

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for GIVLAARI® (givosiran) 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.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section provides the following information[1]:

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 information[1]:

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 of givosiran 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, pharmacokinetics, and pharmacodynamics of givosiran.[2]

One SAE of fatal hemorrhagic pancreatitis was reported in a patient with a complex medical history (obesity, hypertension, bacteremia, and quadriparesis from AIP) and clinical complications due to delayed treatment and hospitalization. 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.[2]

After the SAE, monthly lipase monitoring was initiated in the study. No other cases of pancreatitis or lipase elevations greater than three times the upper limit of the normal range were observed.[2]

Phase 1/2 OLE Study

The Phase 1/2 OLE study (N=16) 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. All patients enrolled in the OLE were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.[3]

During the study, increased lipase was reported as an AE in 4 patients (25%).[3]

ENVISION Study

The ENVISION study (N=94) 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 or placebo once a month for 6 months, followed by an optional 30-month OLE.[4]

During the OLE, increased lipase was reported as an AE in 13 patients (14%).[4]

One patient discontinued givosiran treatment due to SAEs of increased blood homocysteine and pancreatitis.[4]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceutical's global safety database did not identify any new safety concerns for pancreatitis. Pancreatitis remains an important potential risk and is closely monitored through routine pharmacovigilance activities.[5]

ABBREVIATIONS

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

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REFERENCES

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2. Sardh E, Harper P, Balwani M, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. *N Engl J Med*. 2019;380(6):549-558. doi:10.1056/NEJMoa1807838
3. Sardh E, Balwani M, Rees DC, et al. Final results from a phase 1/2, 48-month, open-label extension study of givosiran in patients with acute intermittent porphyria. Presented at: European Association for the Study of the Liver (EASL) Congress; June 21-24, 2023; Vienna, Austria.
4. 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
5. Alnylam Pharmaceuticals. Data on file. MED-ALL-AS1-2400002.