

GIVLAARI[®] (givosiran)

Product Fact Sheet

- GIVLAARI[®] (givosiran) injection for subcutaneous use is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with acute hepatic porphyria (AHP).
 - GIVLAARI is the world's first-ever approved GalNAc-conjugate RNAi therapeutic and Alnylam's second RNA interference (RNAi) therapeutic to be approved in less than two years.
- AHP is a family of rare, genetic diseases characterized by debilitating, potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life.^{1,2,3}
- In the largest interventional study of AHP, GIVLAARI was shown to significantly reduce the rate of porphyria attacks that required hospitalizations, urgent healthcare visits, or intravenous (IV) hemin administration at home.
- GIVLAARI works by specifically reducing the elevated levels of aminolevulinic acid synthase 1 (*ALAS1*) messenger RNA (mRNA) in the liver, leading to reduction of neurotoxins associated with attacks and other disease manifestations of AHP.⁴
- GIVLAARI is a once-monthly subcutaneous injection that is administered by a healthcare professional. The dose of GIVLAARI is determined based on a patient's actual body weight.
 - GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis. GIVLAARI also has a Warning and Precaution for injection site reactions.
- For more information about GIVLAARI, please visit GIVLAARI.com.

GIVLAARI Research at a Glance

- The FDA approval of GIVLAARI was based on positive results from the six-month, randomized, double-blind, placebo-controlled, multinational ENVISION Phase 3 study.⁴
 - The clinical trial enrolled 94 patients with AHP at 36 sites in 18 countries.
 - Patients on GIVLAARI experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo, and similar reduction in IV hemin use, as well as reductions in urinary aminolevulinic acid (ALA) and urinary porphobilinogen (PBG) compared to baseline.
 - The most common adverse reactions (reported in ≥ 20% of patients) with GIVLAARI were nausea (27%) and injection site reactions (25%). Permanent discontinuation occurred in one patient receiving GIVLAARI due to elevated liver transaminases.

Please see Important Safety Information on the following page and full [Prescribing Information](#).





About RNAi Therapeutics

- Historically, RNA was only thought to be involved in protein synthesis. However, in recent years, RNA has been identified to also play significant roles in regulatory functions within the cell.⁵
- A specific class of RNA, called small-interfering RNA (siRNA), appeared to exert cellular control resulting in gene silencing.⁶ In 2001, researchers confirmed that siRNA-mediated gene silencing did occur in human cells.⁷ This form of gene silencing has since become widely known as RNA interference, or RNAi for short.
- The FDA approval of GIVLAARI marks the demonstration of RNAi as a key platform for the development of therapeutics for complex, serious conditions for patients with limited treatment options.

Access to GIVLAARI: Alnylam Assist[®]

As part of Alnylam's commitment to making therapies available, Alnylam Assist[®] offers support services to guide patients through treatment with GIVLAARI, including explaining insurance coverage, financial assistance programs for eligible patients, educational materials to help facilitate conversations with doctors and family, and assistance with connecting to local resources. Patients will have access to an Alnylam Case Manager and Patient Education Liaisons (PELs) throughout their treatment with GIVLAARI. PELs are employees of Alnylam Pharmaceuticals and do not provide medical advice. Alnylam Assist[®] provides support services for patients during their treatment with GIVLAARI. Visit AlnylamAssist.com/GIVLAARI for more information.

IMPORTANT SAFETY INFORMATION

Contraindications

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

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 receiving 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 significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

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 patients receiving GIVLAARI 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 were 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. 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. 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 patients receiving GIVLAARI. To ensure appropriate management, consider acute pancreatitis as a potential diagnosis in patients with signs/symptoms of acute pancreatitis. Consider interruption and/or discontinuation of GIVLAARI treatment for severe cases.

Drug Interactions

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

Adverse Reactions

The most common adverse reactions that occurred in patients receiving GIVLAARI were nausea (27%) and injection site reactions (25%).

For additional information about GIVLAARI, please see full [Prescribing Information](#).

¹Puy et al., *Lancet*. 2010;375:924-937. ²Simon et al., *Patient*. 2018;11:527-37. ³Balwani & Desnick, *Hematology Am Soc Hematol Educ Program*. 2012;2012:19-27. ⁴GIVLAARI [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. ⁵Couzin J. *Science*. 2002;298:2296-7. ⁶Fire A, Xu S, Montgomery MK, et al. *Nature*. 1998;391:806-11. ⁷Elbashir SM, Harborth J, Lendeckel W. *Nature*. 2001;411:494-8.

