Givlaari (givosiran)

NEW PRODUCT SLIDESHOW

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Introduction

- **Brand name:** Givlaari
- **Generic name:** Givosiran
- **Pharmacologic class:** Aminolevulinate synthase 1-directed small interfering RNA
- **Strength and Formulation:** 189mg/mL; soln for SC inj; preservative-free
- **Manufacturer:** Alnylam Pharmaceuticals
- **How supplied:** Single-dose vial—1
- **Legal Classification:** Rx

Givlaari

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Indication

- Treatment of adults with **acute hepatic porphyria**

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Dosage and Administration

- Give by SC inj into the abdomen, the back or side of the upper arms, or the thighs; rotate inj sites
- **2.5mg/kg once monthly**
- For severe or clinically significant transaminase elevations, reduce dose to 1.25mg/kg once monthly
  - If no recurrence, may increase to 2.5mg/kg

Considerations for Special Populations

- **Pregnancy:** no available data to evaluate drug-associated risk
- **Nursing mothers**: no data on presence in human milk
- **Pediatric**: safety, effectiveness not established
- **Geriatrics**: studies did not include sufficient numbers of patients aged 65 years and over to determine if response is different

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Warnings/Precautions

- Have medical support readily available
- **Monitor for anaphylaxis**; discontinue immediately and treat if occurs
- **Obtain LFTs** prior to initiation, repeat monthly during the first 6 months, then as clinically indicated
  - **Interrupt or discontinue therapy if** clinically significant transaminase elevations occur (see Dosing)
  - Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment
- **Monitor renal function**: increases in serum creatinine levels and decreases in eGFR have been reported

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Interactions

- Avoid concomitant use with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities
  - If unavoidable, decrease the dose of substrates

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Adverse Reactions

- **Most frequent (incidence (≥20%)**: nausea, injection site reactions
- **Others**: rash, serum creatinine increased, transaminase elevations, fatigue

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Mechanism of Action

- Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver *ALAS1* mRNA
- This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of acute hepatic porphyria

Pharmacokinetics

- Plasma protein binding: 90%
- Metabolism: primarily metabolized by nucleases to oligonucleotides of shorter lengths; givosiran is not a substrate of CYP enzymes
- Elimination half-life: 6 hours
- Excretion: renal

Clinical Trials

- Double-blind, placebo-controlled trial (ENVISION; NCT03338816)
- 94 patients with acute hepatic porphyria randomized to receive once monthly subcutaneous injections of Givlaari or placebo over 6 months
- **Inclusion criteria**: minimum of 2 porphyria attacks requiring hospitalization, urgent care, or IV hemin administration at home in the 6 months prior to study entry
- Median age: 37.5 years (89% female; 78% white)

Clinical Trials

- Efficacy was measured by the rate of porphyria attacks that required hospitalizations, urgent care visit, or IV hemin administration at home

- On average, Givlaari-treated patients experienced 70% (95% CI, 60-80) fewer porphyria attacks compared with placebo

- **Mean rate of porphyria attacks**: 1.9 (95% CI, 1.3-2.8) with Givlaari (n=48) vs 6.5 (95% CI, 4.5-9.3) with placebo (n=46); **rate ratio**: 0.3 (95% CI, 0.2-0.4); *P* <.0001

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Clinical Trials

- Treatment with Givlaari also resulted in a reduction in hemin use, urinary ALA, and urinary PBG

- **Mean days of hemin use**: 4.7 (95% CI, 2.8-7.9) with Givlaari vs 12.8 (95% CI, 7.6-21.4) with placebo; **ratio:** 0.3 (95% CI, 0.1-0.5); *P* =.0002

New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/givlaari/