GIVLAARI®
(givosiran) injection for subcutaneous use
189 mg/mL

DOSING AND ADMINISTRATION GUIDE

INDICATION

GIVLAARI® (givosiran) is indicated for the treatment of adults with acute hepatic porphyria (AHP).

IMPORTANT SAFETY INFORMATION

Contraindications

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

Please see Important Safety Information on page 7 and full Prescribing Information.

Overview of GIVLAARI® (givosiran)

GIVLAARI is indicated for the treatment of adults with acute hepatic porphyria (AHP).

GIVLAARI is a double-stranded small interfering RNA (RNAi) therapeutic specifically targeting ALAS1 mRNA, reducing ALAS1 mRNA levels and leading to reductions in urinary ALA and PBG.

GIVLAARI dosing[1]

Weight-based dosing with GIVLAARI

The recommended dose of GIVLAARI is 2.5 mg/kg administered via subcutaneous injection once monthly. Dosing is based on actual body weight.

Dose Modification for Adverse Reactions:

In patients with severe or clinically significant transaminase elevations, who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. In patients who resume dosing at 1.25 mg/kg once monthly without recurrence of severe or clinically significant transaminase elevations, the dose may be increased to the recommended 2.5 mg/kg once monthly.

The following chart contains several illustrative dosing calculations. These examples are not intended to replace your clinical judgment. Confirm all calculations prior to GIVLAARI administration.

- GIVLAARI is a ready-to-use solution that does not require additional reconstitution or dilution prior to administration, supplied in single-dose vials of 189 mg/mL
- Calculate volume required based on recommended dosage: patient weight in kg × 2.5 mg/kg × 1 mL/189 mg = mL of GIVLAARI to administer
- If the total volume of GIVLAARI per dose is >1.5 mL, divide the dose into multiple injections of approximately equal volumes

DOSING BY WEIGHT

GIVLAARI DOSE	BODY WEIGHT (kg)	TOTAL DOSE VOLUME* (mL)	NUMBER OF VIALS	INJECTION(S)
2.5 mg/kg	40	0.5		1 injection in a 1-mL syringe
	50	0.7		
	60	0.8		
	70	0.9		
	80	1.1		1 injection in a 3-mL syringe
	90	1.2		
	100	1.3		
	110	1.5		
	120	1.6†		2 injections: **1**. 0.8 mL in a 1-mL syringe **2**. 0.8 mL in a 1-mL syringe

*Volumes rounded to nearest 0.1 mL (eg, 0.55 mL was rounded to 0.6 mL).
†Divide doses requiring volumes >1.5 mL equally into multiple syringes.

Please see Important Safety Information on page 7 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

GIVLAARI® (givosiran) administration instructions[1]

- Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI
- GIVLAARI is intended for subcutaneous use by a healthcare professional only

Supplies needed

Product vial

Sterile syringe(s) (1 mL or 3 mL)

21G or larger needle to withdraw product from vial

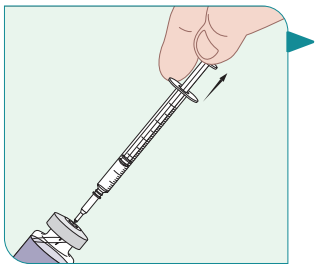
25G or 27G needle with 1/2" or 5/8" length for subcutaneous administration

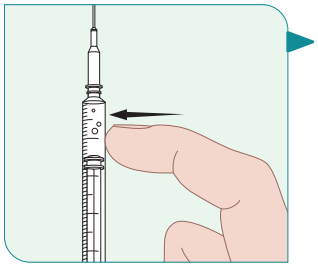
Alcohol swabs

Sharps container for needle disposal

Preparing the GIVLAARI dose[2]

- Use aseptic technique
- Calculate the required volume of GIVLAARI based on the recommended weight-based dosage
- GIVLAARI is a sterile, preservative-free, clear, colorless-to-yellow solution. As with all parenteral drug products, inspect the solution for particulate matter and discoloration prior to administration





1. To withdraw GIVLAARI solution, hold the vial upright or tilt at a slight angle and ensure the flat edge of the needle is pointed downwards
2. Gently draw up the necessary volume(s) of GIVLAARI solution with a 21G or larger needle into either:
   - A sterile 1-mL syringe for volumes up to 1 mL or
   - A sterile 3-mL syringe for volumes >1 mL, up to a maximum of 1.5 mL
3. Point the needle and syringe straight upwards and tap the syringe to move any air bubbles to the top
4. Once the air bubbles are at the top, gently push the plunger to expel the bubbles from the syringe
   - Check to make sure you still have the correct amount of GIVLAARI in the syringe
5. Once the dose is prepared and in the administration syringe(s), replace the 21G or larger needle with either a 25G or 27G needle

- **Note: Do not advance GIVLAARI into the 25G or 27G needle**

IMPORTANT SAFETY INFORMATION (continued)

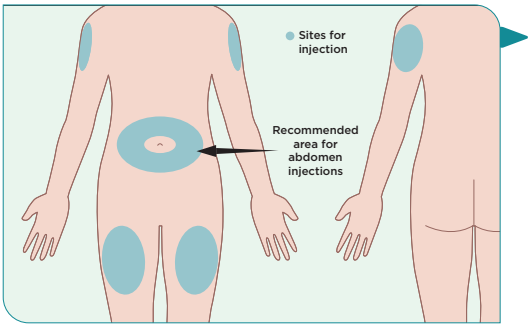
Anaphylactic Reaction

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.

Please see Important Safety Information on page 7 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Choosing and preparing the injection site[1]



- You may inject GIVLAARI® (givosiran) into the abdomen, the back or side of the upper arms, or the thighs
  - Rotate injection sites
  - **Note:**
    - **When administering subcutaneous injections into the abdomen, avoid a 5.0-cm diameter circle around the navel**
    - **If more than one injection is needed for a single dose of GIVLAARI, the injection sites should be at least 2 cm apart from previous injection locations**
  - Clean the area you intend to inject with an alcohol swab and wait for the area to dry completely

DO NOT ADMINISTER INJECTIONS[1]:

- In areas that are **reddened, inflamed,** or **swollen**
- Into **scar tissue**

IMPORTANT SAFETY INFORMATION (continued)

Hepatic Toxicity

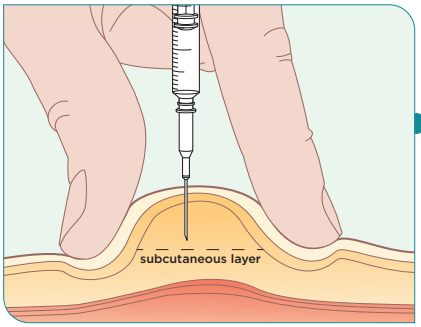
Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients treated with GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

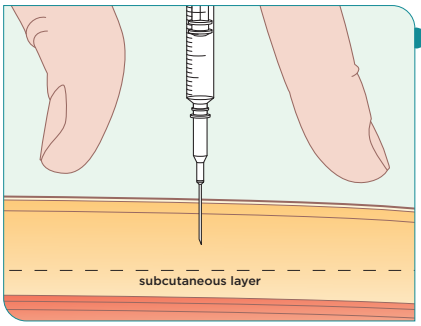
Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have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

Please see Important Safety Information on page 7 and full Prescribing Information.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Administering GIVLAARI[2]





1. Ensure proper injection technique. Do not inject into a vein or muscle
2. With your free hand, pinch the skin at the injection site and insert the needle at a right angle (90 degrees) to deliver the injection just below the skin
   - In patients with little subcutaneous tissue or if the needle size is longer than 1 inch, the needle should be inserted at a 45-degree angle
   - Do not press down on the plunger while piercing the skin
3. Once the needle is inserted through the skin, release the pinched skin and administer the dose in a slow and steady manner
   - **Note: Do not aspirate after inserting the needle to prevent tissue damage, hematoma, and bruising**
4. Once GIVLAARI has been administered, count for at least 5 seconds before withdrawing the needle from the skin
5. Lightly press gauze or cotton ball on the injection site as needed. Do not put the needle cap back on
6. GIVLAARI vials are for single use only. Discard unused portion of the drug. Dispose of needles, syringes, and needle caps in a locally approved sharps disposal container

IN CASE OF A MISSED DOSE[1]:

If a dose is missed, administer GIVLAARI® (givosiran) as soon as possible.
Resume dosing at monthly intervals following administration of the missed dose.

IMPORTANT SAFETY INFORMATION (continued)

Injection Site Reactions

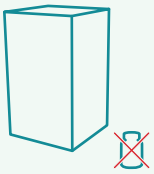
Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

Please see Important Safety Information on page 7 and full Prescribing Information.

How GIVLAARI® (givosiran) is supplied[1]

- GIVLAARI is a ready-to-use solution supplied in single-dose vials of 189 mg/mL in cartons containing one vial

Storage and handling[1]



Keep in carton

Store at 2°C to 25°C (36°F to 77°F)

Do not freeze[2]

References: 1. GIVLAARI [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; **2.** Data on File. Alnylam Pharmaceuticals, Inc; 2019.

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see Important Safety Information on page 7 and full Prescribing Information.

INDICATION

GIVLAARI® (givosiran) is indicated for the treatment of adults with acute hepatic porphyria (AHP).

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).

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.

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

For more information about GIVLAARI® (givosiran), please contact Alnylam Medical Information.

By phone:
1-877-ALNYLAM (1-877-256-9526)

Or email:
medinfo@alnylam.com

Alnylam® PHARMACEUTICALS

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL