STARTING YOUR JOURNEY *with* GIVLAARI® (givosiran)

What is GIVLAARI® (givosiran)?

GIVLAARI is a prescription medicine used to treat acute hepatic porphyria (AHP) in adults.

IMPORTANT SAFETY INFORMATION

Do not use GIVLAARI if you have ever had a severe allergic reaction to GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

"Having fewer attacks has helped me live in the moment and just dream of what my life could be."

Amalia, an artist and Alnylam Patient Ambassador on GIVLAARI

Individual results may vary.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause severe allergic reaction:

Tell your doctor or nurse right away if you experience any of the following signs or symptoms of a severe allergic reaction during treatment:

- Swelling – mainly of the lips, tongue or throat which makes it difficult to swallow or breathe
- Breathing problems or wheezing
- Feeling dizzy or fainting
- Rash or hives
- Itching

If you have a severe allergic reaction, your doctor or nurse will stop GIVLAARI treatment right away and you may need to take other medicines to control the symptoms.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

YOUR GIVLAARI® (givosiran) JOURNEY STARTS HERE

Now that you and your doctor have decided to start you on GIVLAARI, this guide may help you understand more about your treatment and the **patient support services available to you through Alnylam Assist®**.

1

Get started by finding a notebook or using the provided treatment journal. Tracking your journey can be **easier with these tips**:

- Use your GIVLAARI treatment journal to record your injections and how you're feeling
- Set up daily journal reminders on your phone
- Ask a caregiver to help you stay on track
- Create entries on specific days and times of the week

2

Think about how you're feeling **throughout the day,** and write down answers to questions like:

- Are you in pain? Where? How would you describe it?
- Are you feeling anything else unusual? What and where?
- Are you having any other symptoms that you would like to talk to your doctor about?

3

Enter your **feelings and observations every day**.

Before each doctor visit, review your journal entries and use them to **help discuss your treatment journey** when you're at your appointment.

KEEP TRACK OF YOUR JOURNEY

Take note of possible triggers

When you experience symptoms, take notes on the factors that may be affecting your condition. Common triggers for attacks are shown below:

- Some medications
- Emotional stress
- Hormones (menstrual cycle)
- Alcohol
- Smoking
- Physical stress caused by extreme dieting, illness, or surgery

Since triggers can be different for every person, there may be others not listed here.

YOUR SYMPTOMS AND TRIGGERS

1. What are your most disruptive symptoms?

_____

_____

2. How frequently do you experience the symptoms above? ***Please circle one:***

Daily Weekly Monthly Several times a year

3. Do any of the following triggers make your acute hepatic porphyria (AHP) symptoms feel more severe? ***Check all that apply:***

- ☐ Medications
- ☐ Emotional stress
- ☐ Surgery
- ☐ Other: _____
- ☐ Hormones (menstrual cycle)
- ☐ Physical stress caused by illness or surgery
- ☐ Alcohol
- ☐ Smoking

Be sure to track the ways your symptoms or triggers change as you continue treatment with GIVLAARI® (givosiran).

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause liver problems:

Your doctor will check your liver function by doing blood tests:

- Before you start using GIVLAARI
- Once a month for the first 6 months of treatment
- And when they think it is needed

If these tests show abnormal results, your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

"Alnylam Assist®, and our Case Manager, really helped us navigate the approval process."

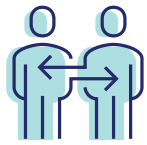
Amalia, an artist and Alnylam Patient Ambassador on GIVLAARI

Individual results may vary.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

REMEMBER, YOU ARE NOT ALONE



LEARN FROM AN ALNYLAM PATIENT EDUCATION LIAISON (PEL)

PELs are employees of Alnylam Pharmaceuticals. They are not acting as healthcare providers and are not part of your healthcare team.

An Alnylam PEL can:

- Provide you with disease education
- Connect you to additional resources
- Help you understand how GIVLAARI® (givosiran) works

SPEAK WITH AN ALNYLAM CASE MANAGER

An Alnylam Case Manager can:

- Help you understand your insurance benefits
- Determine your eligibility for Alnylam financial assistance programs*
- Provide you with product support throughout your treatment

Alnylam Assist® contact information

Alnylam PEL

Name: _____

Phone Number: _____

Alnylam Case Manager

Name: _____

Phone Number: _____

For more information, please visit www.GIVLAARIpel.com, or call 1-833-256-2748

*Individuals must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the programs at any time.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

HOW ALNYLAM ASSIST® CAN HELP

To start the process, complete a Start Form with your doctor.

STEP 1: Receive a welcome call	Within 2 business days after receiving a completed Start Form, an **Alnylam Case Manager will reach out to discuss**: • Communication preferences • Where to send your Starter Kit • Insurance information
STEP 2: Connect with a PEL	An Alnylam Case Manager will also provide you the opportunity to **connect with an Alnylam PEL**, who can provide information about AHP and answer questions you may have about GIVLAARI® (givosiran).
STEP 3: Understand insurance benefits	An Alnylam Case Manager will work with your insurance company to understand your coverage and determine if there are any out-of-pocket treatment costs. They can also assess if you are eligible for **Alnylam's financial assistance programs**.*
STEP 4: Get ready for your first appointment	An Alnylam Case Manager may help identify where you'll receive treatment. You will schedule your first treatment based on your **doctor's recommendations and your schedule**.
STEP 5: Ongoing support	After your first treatment, an Alnylam Case Manager or PEL can check in with you at other times during your treatment journey. They will tailor their method of communication to what works best for you.

Talk to your doctor to determine if home administration is right for you. Your Alnylam Case Manager can check your insurance eligibility for administration by a healthcare provider at home†

AHP=acute hepatic porphyria; PEL=Patient Education Liaison.

*Individuals must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the programs at any time.

†Home administration may not be covered by all insurance plans.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

YOUR GIVLAARI® (givosiran) TREATMENT ROUTINE

GIVLAARI is intended to reduce acute hepatic porphyria (AHP) attacks in adults and should be taken regularly. It's important to receive your injection on time every month. A consistent routine and adhering to your doctor's treatment plan can help you get the most out of GIVLAARI.

Keep in mind the following to help you adjust to your new routine:

- **Schedule appointments in advance** to help plan around your schedule
  - GIVLAARI is intended to be taken monthly
- **Every patient responds to GIVLAARI differently**
- **Compare your journal notes from month to month** to see any potential changes in your health
- **Consult your doctor if you have questions**

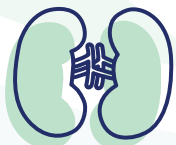
Keep your *GIVLAARI Journal* handy—bring it to appointments to help track and share what matters.

IMPORTANT SAFETY INFORMATION: MONITORING

GIVLAARI can cause liver problems, kidney problems, and increased homocysteine (a type of amino acid) levels. Throughout your treatment, your doctor will monitor these areas by doing blood tests.

Liver Monitoring

Your liver function will be monitored before starting GIVLAARI, every month for the first 6 months, and then as requested by your doctor or nurse. If your tests show abnormal results, your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.



Kidney Monitoring

Throughout treatment, your doctor will check to make sure your kidneys are working properly.

Homocysteine Monitoring

Your doctor will check your homocysteine levels before and during treatment with GIVLAARI. If your homocysteine levels increase, your doctor may also check your folate, vitamin B6, and vitamin B12 levels and suggest taking a vitamin B6 supplement.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

"Getting injections that fit with my schedule, and my life not being dictated by attacks anymore, is one of the best parts."

Hannah, patient on GIVLAARI

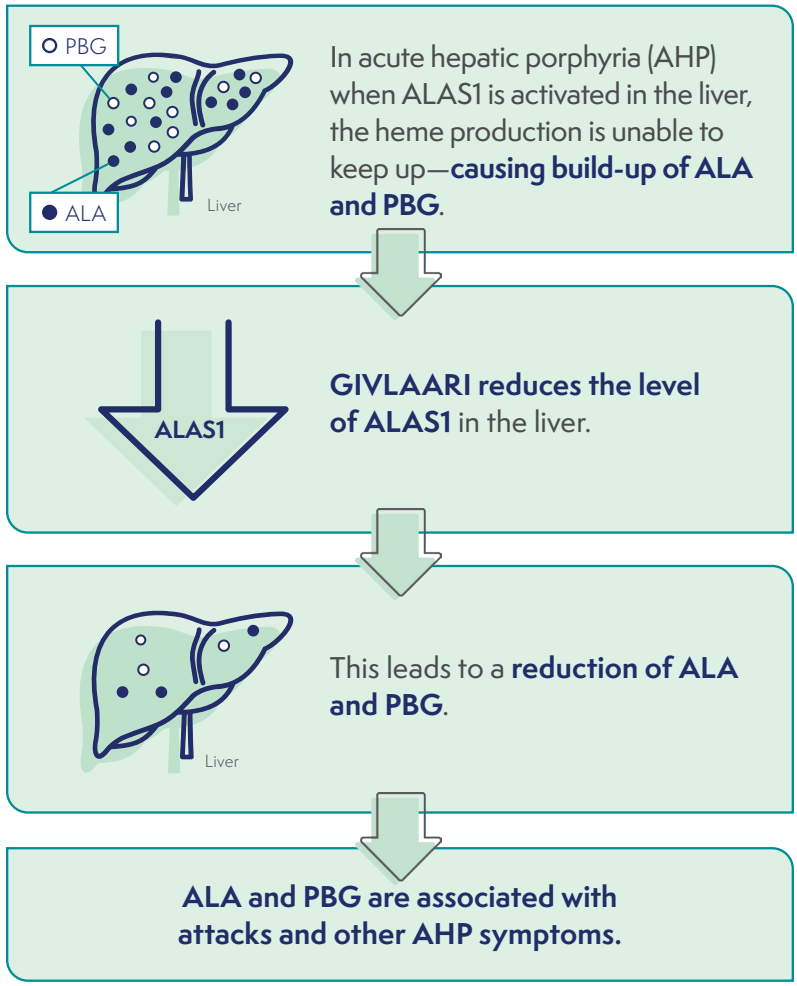
Individual results may vary.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

HOW GIVLAARI® (givosiran) WORKS

GIVLAARI reduces the amount of ALAS1 in the liver, which leads to a reduction in levels of the toxins ALA and PBG.



To see more, visit www.GIVLAARI.com/about-ahp or scan the QR code

ALA=delta-aminolevulinic acid; ALAS1=delta-aminolevulinic acid synthase 1; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause kidney problems:

Your doctor will check how your kidneys are working while you are using GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

WHAT TO KNOW ABOUT YOUR GIVLAARI® (givosiran) INJECTION

GIVLAARI is a once-a-month injection that is given subcutaneously (under the skin) by a healthcare professional.

IMPORTANT SAFETY INFORMATION: ABOUT YOUR INJECTION

GIVLAARI can cause severe allergic reactions and injection site reactions. Tell your healthcare provider right away if you experience any of the following:

Signs of an allergic reaction, including:

- Swelling of the lips, tongue, or throat that makes it difficult to swallow or breathe
- Breathing problems or wheezing
- Feeling dizzy or fainting
- Rash or hives
- Itching

If you have a severe allergic reaction, your doctor or nurse will stop GIVLAARI treatment right away. You may need to take other medicines to control the symptoms.

Reaction at the injection site, including:

- Redness
- Pain
- Itchiness
- Rash
- Discoloration
- Swelling

Consider asking your healthcare provider about rotating injection sites

You may receive an injection in the abdomen, thigh, or the side or back of the upper arm.

Track your injection site locations and how you're feeling in your GIVLAARI Treatment Journal

Keep in mind that everyone's experience may differ, and the results shown in this brochure are what was seen in clinical trials. Before and during your treatment, be sure to discuss questions or concerns with your doctor.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause injection site reactions:

GIVLAARI is given as an injection under the skin (called a "subcutaneous injection"). Reactions to this injection may happen during treatment with GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

In a 6-month study,

PATIENTS TAKING GIVLAARI® (givosiran) EXPERIENCED FEWER AHP ATTACKS

70% **fewer attacks**

on average, compared to those who received placebo

- **GIVLAARI was studied** in adults with acute hepatic porphyria (AHP) who were experiencing recurrent* AHP attacks
  - Attacks measured in the study were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home
- **At 6 months,** the results in 48 patients who received GIVLAARI were compared to those of 46 patients who received placebo (an injection that did not contain medicine)
  - After the first 6 months of treatment, patients on GIVLAARI had an average of 1.9 AHP attacks compared to 6.5 for those on placebo

*Patients experienced at least 2 attacks in the 6 months prior to starting in the study.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause injection site reactions (cont'd):

Tell your doctor or nurse right away if you experience any of the following symptoms of an injection site reaction during treatment: redness, pain, itchiness, rash, discoloration, or swelling around the injection site.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

In the same study,

PATIENTS TAKING GIVLAARI® (givosiran) REQUIRED FEWER DAYS OF HEMIN USE

fewer days of hemin use

to treat AHP attacks, on average, compared to those on placebo

- **At 6 months, patients on GIVLAARI** had an average of 4.7 days of hemin use compared to 12.8 days for patients on placebo
- **In the study, patients who experienced an attack** were treated according to local standards of care, which could include hemin
- **Using hemin to prevent an attack** was not allowed during the study

AHP=acute hepatic porphyria.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause increased blood homocysteine levels:

GIVLAARI may cause increased levels of homocysteine (a type of amino acid) in your blood. Your doctor will check your homocysteine levels before and during treatment by doing blood tests. If your levels are increased, your doctor may check your folate, vitamins B12 and B6, and tell you to take a vitamin B6 supplement.

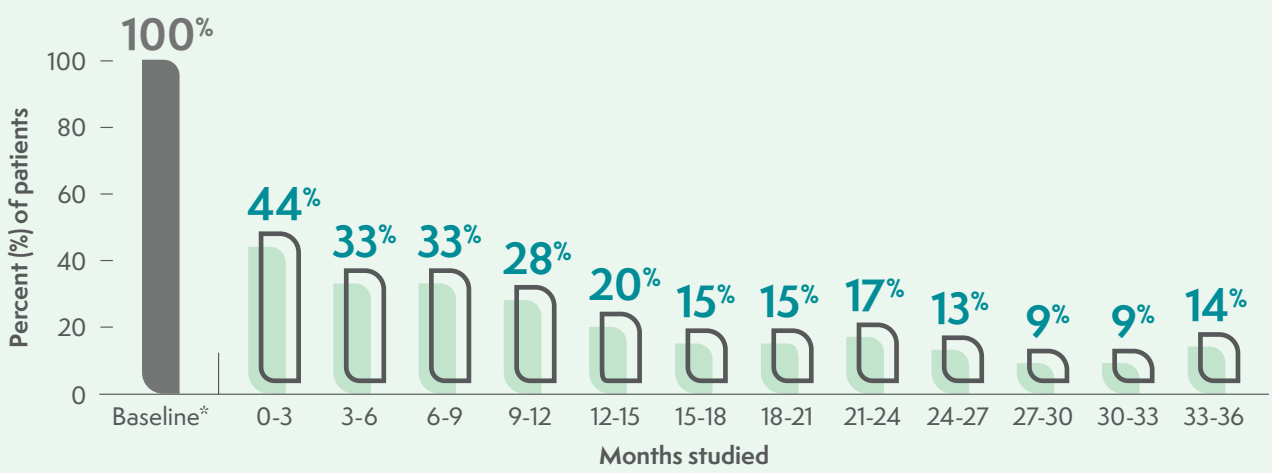
Please see Important Safety Information on page 17 and full Prescribing Information.

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

FEWER PATIENTS EXPERIENCED AHP ATTACKS OVER 36 MONTHS

After the 6-month study, the 93 eligible patients who remained in the study received GIVLAARI® (givosiran) once a month.

The graph below shows the 48 patients who were treated with GIVLAARI in the 6-month study and continued treatment for 36 months. Over time, fewer patients had attacks.



*All patients experienced at least 2 attacks in the 6 months prior to starting in the study.

Attacks measured in the study were defined as those that required hospitalization, urgent healthcare visit, or IV (intravenous) hemin administration at home.

These results were observed in the clinical trial. Keep in mind that everyone responds to GIVLAARI differently.

AHP=acute hepatic porphyria.

IMPORTANT SAFETY INFORMATION

GIVLAARI can cause inflammation of the pancreas (pancreatitis):

Cases of acute pancreatitis including some that were severe, have been reported in patients receiving GIVLAARI. If you have a severe case of acute pancreatitis your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

"Now, I don't fear as much having a surprise attack and, with the support of my care team, feel like I can quit planning my life around porphyria."

Colin, an Alnylam Patient Ambassador on GIVLAARI

Individual results may vary.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

SAFETY PROFILE OF GIVLAARI® (givosiran)

Safety during the first 6 months of the study

- In the first 6 months of the study, 1 patient taking GIVLAARI stopped treatment due to changes in liver function. No patients taking placebo stopped treatment

The most common side effects in patients treated with GIVLAARI compared to those taking placebo in the first 6 months of the study were:

	GIVLAARI (48 patients)	Placebo (46 patients)
Nausea	27%	11%
Injection site reactions	25%	0%
Rash	17%	4%
Changes in kidney function	15%	4%
Changes in liver function	13%	2%
Fatigue	10%	4%

Safety through month 36 of the study

- The most frequently reported side effects occurring in ≥20% of patients were injection site reactions, nausea, fatigue, nasopharyngitis, headache, urinary tract infection, and upper respiratory tract infection
- Increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI

Please see Important Safety Information on page 17 and full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Do not use GIVLAARI if you have ever had a severe allergic reaction to GIVLAARI.

GIVLAARI can cause:

- **Severe allergic reaction**

Tell your doctor or nurse right away if you experience any of the following signs or symptoms of a severe allergic reaction during treatment:

- Swelling – mainly of the lips, tongue or throat which makes it difficult to swallow or breathe
- Breathing problems or wheezing
- Feeling dizzy or fainting
- Rash or hives
- Itching

If you have a severe allergic reaction, your doctor or nurse will stop GIVLAARI treatment right away and you may need to take other medicines to control the symptoms.

- **Liver problems**

Your doctor will check your liver function by doing blood tests:

- Before you start using GIVLAARI
- Once a month for the first 6 months of treatment
- And when they think it is needed

If these tests show abnormal results, your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

- **Kidney problems**

Your doctor will check how your kidneys are working while you are using GIVLAARI.

- **Injection site reactions**

GIVLAARI is given as an injection under the skin (called a "subcutaneous injection"). Reactions to this injection may happen during treatment with GIVLAARI.

Tell your doctor or nurse right away if you experience any of the following symptoms of an injection site reaction during treatment: redness, pain, itchiness, rash, discoloration, or swelling around the injection site.

- **Increased blood homocysteine levels**

GIVLAARI may cause increased levels of homocysteine (a type of amino acid) in your blood. Your doctor will check your homocysteine levels before and during treatment by doing blood tests. If your levels are increased, your doctor may check your folate, vitamins B12 and B6, and tell you to take a vitamin B6 supplement.

- **Inflammation of the pancreas (pancreatitis)**

Cases of acute pancreatitis including some that were severe, have been reported in patients receiving GIVLAARI. If you have a severe case of acute pancreatitis your doctor or nurse will decide whether to temporarily interrupt or stop treatment with GIVLAARI.

What are the common side effects of GIVLAARI?

The most common side effects of GIVLAARI are nausea and injection site reactions. These are not all the possible side effects of GIVLAARI. Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

For additional information about GIVLAARI, please see the full Prescribing Information.

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

FREQUENTLY ASKED QUESTIONS

Can GIVLAARI® (givosiran) be used for any type of acute hepatic porphyria (AHP)?

GIVLAARI is a prescription medicine used to treat AHP in adults. There are 4 types of AHP:

- **Acute intermittent porphyria (AIP)**
- **Hereditary coproporphyria (HCP)**
- **Variegate porphyria (VP)**
- **ALAD-deficiency porphyria (ADP)**

Most patients in GIVLAARI clinical studies had AIP, the most common type of AHP.

How is GIVLAARI given?

GIVLAARI is given once a month as a subcutaneous injection (under the skin) by a healthcare professional.

Please see page 11 for additional information about your GIVLAARI injection.

Will I need any tests while taking GIVLAARI?

Throughout your treatment with GIVLAARI, your doctor will monitor your liver, kidneys, and homocysteine (a type of amino acid) levels by doing blood tests.

Please see page 8 for more information about monitoring.

What should I do if I miss a dose of GIVLAARI?

If you miss a dose, talk to your doctor about scheduling your next dose as soon as possible.

ALAD=delta-aminolevulinic acid dehydratase.

IMPORTANT SAFETY INFORMATION

What are the common side effects of GIVLAARI?

The most common side effects of GIVLAARI are nausea and injection site reactions. These are not all the possible side effects of GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

Can I use hemin while using GIVLAARI® (givosiran)?

In clinical studies of GIVLAARI, some people on GIVLAARI used hemin to treat acute hepatic porphyria attacks. Use of GIVLAARI with regularly scheduled (prophylactic) hemin was not studied in clinical trials of GIVLAARI. Talk to your doctor if you have questions about your treatment plan.

Is GIVLAARI safe to use during pregnancy?

GIVLAARI has not been studied in women who are pregnant. If you are pregnant or plan to become pregnant, it is important to discuss your treatment plan with your doctor.

I have a question not listed here. What should I do?

For anything urgent, please contact your doctor right away. For everything else, please write down your questions below so you can bring it up at your next doctor appointment.

QUESTIONS FOR YOUR DOCTOR

1. _____

_____

2. _____

_____

3. _____

_____

4. _____

_____

IMPORTANT SAFETY INFORMATION

What are the common side effects of GIVLAARI? (cont'd)

Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see Important Safety Information on page 17 and full Prescribing Information.

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

REMEMBER, YOU ARE NOT ALONE

No matter where you are on your treatment journey, you may still have questions about GIVLAARI® (givosiran).

An Alnylam Patient Education Liaison (PEL) can provide educational information. Connect with a PEL through www.GIVLAARIpel.com.

PELs can provide information about acute hepatic porphyria (AHP) and GIVLAARI, but you should always discuss your health concerns and treatment choices with your doctor. Use the pages inside to get your thoughts started, and contact your doctor directly if you have anything urgent to report.

The purpose of the Alnylam PELs is to provide education to patients, their families, and caregivers. PELs are employees of Alnylam Pharmaceuticals. They are not acting as healthcare providers and are not part of your healthcare team. PELs do not provide medical care or advice. All diagnosis and treatment decisions should be made by you and your doctor.

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

Want to know more? Please scan the QR code to visit www.GIVLAARI.com for more information.

What is GIVLAARI® (givosiran)?

GIVLAARI is a prescription medicine used to treat acute hepatic porphyria (AHP) in adults.

IMPORTANT SAFETY INFORMATION

Do not use GIVLAARI if you have ever had a severe allergic reaction to GIVLAARI.

Please see Important Safety Information on page 17 and full Prescribing Information.

Alnylam® PHARMACEUTICALS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GIVLAARI® safely and effectively. See full prescribing information for GIVLAARI.

GIVLAARI (givosiran) injection, for subcutaneous use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Pancreatitis (5.6) 4/2024

----------INDICATIONS AND USAGE----------
GIVLAARI is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP). (1)

---------- DOSAGE AND ADMINISTRATION ----------
The recommended dose of GIVLAARI is 2.5 mg/kg once monthly by subcutaneous injection. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 189 mg/mL in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
Severe hypersensitivity to givosiran. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Anaphylactic Reaction: Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms. If anaphylaxis occurs, discontinue GIVLAARI and administer appropriate medical treatment. (5.1)
- Hepatic Toxicity: Measure liver function at baseline and periodically during treatment with GIVLAARI. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. (2.1, 5.2)
- Renal Toxicity: Monitor renal function during treatment with GIVLAARI as clinically indicated. (5.3)
- Injection Site Reactions: May occur, including recall reactions. Monitor for reactions and manage clinically as needed. (5.4)
- Blood Homocysteine Increased: Measure blood homocysteine at baseline and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine, consider supplementation with vitamin B6 (as monotherapy or multivitamin). (5.5)
- Pancreatitis: Consider acute pancreatitis as a potential diagnosis in GIVLAARI-treated patients with acute upper abdominal pain, clinically significant elevation of pancreatic enzymes and/or imaging findings of acute pancreatitis, to ensure appropriate management. (5.6)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (≥20% of patients) included nausea and injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Sensitive CYP1A2 and CYP2D6 Substrates: Avoid concomitant use with CYP1A2 and CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

Missed Dose

Administer GIVLAARI as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose.

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 *[see Warnings and Precautions (5.2)]*. 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 dose of 2.5 mg/kg once monthly.

2.2 Administration Instructions

Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI *[see Warnings and Precautions (5.1)].*

GIVLAARI is intended for subcutaneous use by a healthcare professional only.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GIVLAARI is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-dose vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.

Use aseptic technique.

- Calculate the required volume of GIVLAARI based on the recommended weight-based dosage *[see Dosage and Administration (2.1)]*.
- Withdraw the indicated injection volume of GIVLAARI using a 21-gauge or larger needle.
    - Divide doses requiring volumes greater than 1.5 mL equally into multiple syringes.
- Replace the 21-gauge or larger needle with either a 25-gauge or 27-gauge needle with 1/2” or 5/8” needle length.
- Avoid having GIVLAARI on the needle tip until the needle is in the subcutaneous space.
- Administer injection into the abdomen, the back or side of the upper arms, or the thighs. Rotate injection sites. An injection should never be given into scar tissue or areas that are reddened, inflamed, or swollen.
    - If injecting into the abdomen, avoid a 5 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.
- Discard unused portion of the drug.

3 DOSAGE FORMS AND STRENGTHS

Injection: 189 mg/mL clear, colorless-to-yellow solution in a single-dose vial

4 CONTRAINDICATIONS

GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis *[see Warnings and Precautions (5.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials) *[see Adverse Reactions (6.1)]*. 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.

5.2 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 *[see Adverse Reactions (6.1)]*. 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. For resumption of dosing after interruption, *see Dosage and Administration (2.1)*.

5.3 Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI *[see Adverse Reactions (6.1)]*. In the placebo-controlled study, 15% of the patients in the GIVLAARI arm 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.

5.4 Injection Site Reactions

Injection site reactions have been 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. Among 12 patients with reactions, the highest severity of the reaction was mild among 11 (92%) patients and moderate in one (8%) patient. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration *[see Adverse Reactions (6.1)]*.

5.5 Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI *[see Adverse Reactions (6.1)]*. 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. The clinical relevance of the elevations in blood homocysteine during treatment with GIVLAARI is unknown. 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).

5.6 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Anaphylactic Reaction *[see Warnings and Precautions (5.1)]*
- Transaminase Elevations *[see Warnings and Precautions (5.2)]*
- Serum Creatinine Increase *[see Warnings and Precautions (5.3)]*
- Injection Site Reactions *[see Warnings and Precautions (5.4)]*
- Blood Homocysteine Increased *[see Warnings and Precautions (5.5)]*
- Pancreatitis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the pivotal placebo-controlled, double-blind study (ENVISION), 48 patients received 2.5 mg/kg GIVLAARI and 46 patients received placebo, administered once monthly via subcutaneous injection for up to 6 months. Patients received GIVLAARI for a median of 5.5 months (range 2.7-6.4 months). Of these, 47 patients received ≥5 months of treatment. The most frequently occurring (≥20% incidence) adverse reactions reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%). Permanent discontinuation occurred in one patient due to elevated transaminases.

Table 1: Adverse Reactions that Occurred at Least 5% More Frequently in Patients Treated with GIVLAARI Compared to Patients Treated with Placebo

Adverse Reaction	**GIVLAARI N=48 N (%)**	**Placebo N=46 N (%)**
Nausea	13 (27)	5 (11)
Injection site reactions	12 (25)	0
Rash*	8 (17)	2 (4)
Serum creatinine increase†	7 (15)	2 (4)
Transaminase elevations	6 (13)	1 (2)
Fatigue	5 (10)	2 (4)
* Grouped term includes pruritus, eczema, erythema, rash, rash pruritic, urticaria † Grouped term includes blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease (decreased eGFR)		

Adverse reactions observed at a lower frequency occurring in placebo-controlled and open-label clinical studies included anaphylactic reaction (one patient, 0.9%) and hypersensitivity (one patient, 0.9%).

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 *[see Warnings and Precautions (5.5)]*.

6.2 Immunogenicity

As with all oligonucleotides, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In placebo-controlled and open-label clinical studies, 1 of 111 patients with AHP (0.9%) developed treatment-emergent anti-drug antibodies (ADA) during treatment with GIVLAARI. No clinically significant

differences in the clinical efficacy, safety, pharmacokinetic, or pharmacodynamic profiles of GIVLAARI were observed in the patient who tested positive for anti-givosiran antibodies.

6.3 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

7 DRUG INTERACTIONS

7.1 Effect of GIVLAARI on Other Drugs

Sensitive CYP1A2 and CYP2D6 Substrates

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates *[see Clinical Pharmacology (12.3)]*, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal reproduction studies, subcutaneous administration of givosiran to pregnant rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses that produced maternal toxicity *(see Data).*

There are no available data with GIVLAARI use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider the benefits and risks of GIVLAARI for the mother and potential adverse effects to the fetus when prescribing GIVLAARI to a pregnant woman.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Porphyria attacks during pregnancy, often triggered by hormonal changes, occur in 24% to 95% of AHP patients, with maternal mortality ranging from 2% to 42%. Pregnancy in AHP patients is associated with higher rates of spontaneous abortion, hypertension and low birth weight infants.

Data

Animal Data

In an embryo-fetal development study in pregnant rabbits, givosiran was administered subcutaneously at doses of 0.5, 1.5, and 5 mg/kg/day during organogenesis (gestational days 7-19) or 20 mg/kg as a single administration on gestation day 7. Administration of givosiran was maternally toxic based on decreased body weight gain at all dose levels tested and resulted in increased postimplantation loss starting at 1.5 mg/kg/day. An increased incidence of skeletal variations of the sternebrae was observed at 20 mg/kg. The 1.5 mg/kg/day dose in rabbits is 5 times the maximum recommended human dose (MRHD) of 2.5 mg/kg/month normalized to 0.089 mg/kg/day, based on body surface area. In a combined fertility and embryo-fetal development study in female rats, givosiran was administered subcutaneously at doses of 0.5 to 5 mg/kg/day during organogenesis (gestational days 6-17). The 5 mg/kg/day dose (9 times the normalized MRHD based on body surface area) was associated with a skeletal variation (incomplete ossification of pubes) and produced maternal toxicity.

In a pre- and postnatal development study, givosiran administered subcutaneously to pregnant rats on gestation days 7, 13, and 19 and postnatal days 6, 12, and 18 at doses up to 30 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of GIVLAARI in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GIVLAARI and any potential adverse effects on the breastfed child from GIVLAARI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

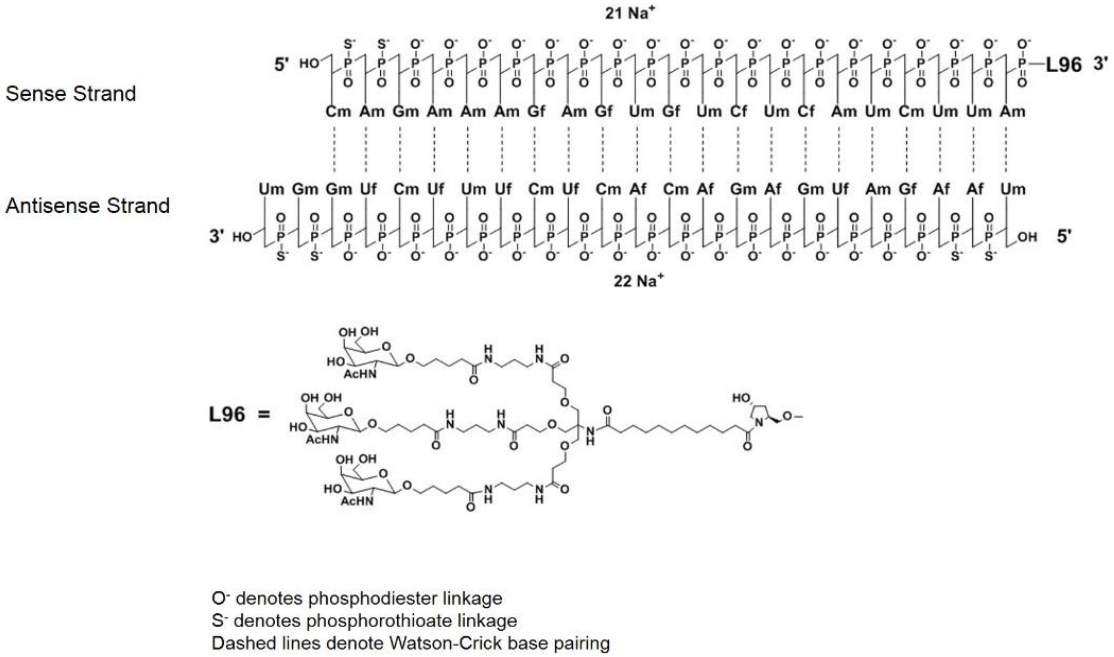
8.5 Geriatric Use

Clinical studies of GIVLAARI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

GIVLAARI is an aminolevulinate synthase 1-directed small interfering RNA (siRNA), covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

The structural formulas of the givosiran drug substance in its sodium form, and the ligand (L96), are presented below.



Abbreviations: Af = adenine 2'-F ribonucleoside; Cf = cytosine 2'-F ribonucleoside; Uf = uracil 2'-F ribonucleoside; Am = adenine 2'-OMe ribonucleoside; Cm = cytosine 2'-OMe ribonucleoside; Gf = guanine 2'-F ribonucleoside; Gm = guanine 2'-OMe ribonucleoside; Um = uracil 2'-OMe ribonucleoside; L96 = triantennary GalNAc (N-acetylgalactosamine)

GIVLAARI is supplied as a sterile, preservative-free, 1-mL colorless-to-yellow solution for subcutaneous injection containing 189 mg givosiran in a single-dose, 2-mL Type 1 glass vial with a fluoropolymer-coated rubber stopper and a flip-off aluminum seal. GIVLAARI is available in cartons containing one single-dose

vial each. GIVLAARI is formulated in Water for Injection. Sodium hydroxide and/or phosphoric acid may have been added for pH adjustment during product manufacturing.

The molecular formula of givosiran sodium is C_{524} H_{651} F_{16} N_{173} Na_{43} O_{316} P_{43} S_6 with a molecular weight of 17,245.56 Da.

The molecular formula of givosiran (free acid) is C_{524} H_{694} F_{16} N_{173} O_{316} P_{43} S_6 with a molecular weight of 16,300.34 Da.

12 CLINICAL PHARMACOLOGY

12.1 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 AHP.

12.2 Pharmacodynamics

The pharmacodynamic effects of GIVLAARI were evaluated in chronic high excreters treated with 0.035 to 2.5 mg/kg single dose and AHP patients treated with 2.5 to 5 mg/kg once monthly and 2.5 to 5 mg/kg once quarterly dose via subcutaneous injection. Dose-dependent reduction in urinary *ALAS1* mRNA, ALA and PBG levels was observed over the 0.035 to 5 mg/kg dose range (0.14 to 2-fold the approved recommended dosage). Median reductions from baseline in urinary ALA and PBG of 83.7% and 75.1%, respectively, were observed 14 days after the first dose of GIVLAARI 2.5 mg/kg once monthly in AHP patients. Maximal reductions in ALA and PBG levels were achieved around Month 3, with median reductions from baseline of 93.8% for ALA and 94.5% for PBG, and were sustained thereafter with repeated once monthly dosing.

Cardiac Electrophysiology

The effect of GIVLAARI on the QTc interval was evaluated in a double-blind, placebo-controlled study and the open-label extension in 94 patients. No large mean increase in QTc (i.e. >20 ms) was detected at the 2.5 mg/kg once monthly dose level. A dedicated thorough QT study has not been conducted with GIVLAARI.

12.3 Pharmacokinetics

The pharmacokinetics of givosiran and its active metabolite [AS(N-1)3′ givosiran] were evaluated following single and multiple dosing in chronic high excreter subjects and AHP patients as summarized in Table 2.

Table 2. Pharmacokinetic Parameters of Givosiran and Its Active Metabolite

		Givosiran	AS(N-1)3′ Givosiran
General Information			
Steady-State Exposure	**C_{max} [Mean (CV%)]**	321 ng/mL (51%)	123 ng/mL (64%)
	AUC_{24} [Mean (CV%)]	4130 ng·h/mL (43%)	1930 ng·h/mL (63%)
Dose Proportionality		• Steady-state maximum plasma concentration (C_{max}) and area under the curve (AUC) for givosiran and AS(N-1)3′ givosiran increase proportionally over the 0.35 mg/kg to 2.5 mg/kg once monthly dose range (0.14 to 1-fold the approved recommended dosage). • C_{max} and AUC for givosiran and AS(N-1)3′ givosiran increase slightly greater than proportionally at doses greater than 2.5 mg/kg once monthly.	
Accumulation		• No accumulation of givosiran or AS(N-1)3′ givosiran was observed following multiple dosing.	
Absorption			
T_{max} [Median (range)]		3 (0.5-8) hours	7 (1.5-12) hours
Distribution			
Apparent Central Volume of Distribution (Vz/F) [Mean (RSE%)][a]		10.4 L (2.3%)	
Protein Binding		90%[b]	Not evaluated
Organ Distribution		Givosiran and AS(N-1)3′ givosiran distribute primarily to the liver after subcutaneous dosing.	
Elimination			
Half-Life [Mean (CV%)]		6 hours (46%)	6 hours (41%)
Apparent Clearance [Mean (CV%)][a]		35.1 L/hr (18%)	64.7 L/hr (33%)
Metabolism			
Primary Pathway		Givosiran is metabolized by nucleases to oligonucleotides of shorter lengths. Givosiran is not a substrate of CYP enzymes[c].	
Active Metabolite		The active metabolite, AS(N-1)3′ givosiran, is equipotent to givosiran in plasma and the AUC_{0-24} represents 45% of givosiran AUC, at the approved recommended givosiran dosage.	
Excretion			
Primary Pathway		The dose recovered in urine was 5%-14% as givosiran and 4%-13% as AS(N-1)3′ givosiran[d].	

[a] Based on population PK model estimation.
[b] Givosiran plasma protein binding was concentration-dependent and decreased with increasing givosiran concentrations (from 92% at 1 µg/mL to 21% at 50 µg/mL).
[c] Based on in vitro study result.
[d] After single and multiple subcutaneous doses of givosiran 2.5 mg/kg and 5 mg/kg.

Specific Populations

No clinically meaningful differences in givosiran pharmacokinetics or pharmacodynamics (percent reduction in urinary ALA and PBG) were observed based on age (19 to 65 years), sex, race/ethnicity, mild, moderate or severe renal impairment (eGFR ≥15 to <89 mL/min/1.73m^2 estimated by the Modification of Diet in Renal Disease [MDRD] formula), and mild hepatic impairment (bilirubin ≤1×ULN and AST >1×ULN, or bilirubin >1×ULN to 1.5×ULN).The effect of end-stage renal disease (eGFR <15 mL/min/1.73m^2), and moderate to severe hepatic impairment on givosiran pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Effect of givosiran on CYP1A2 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased caffeine (sensitive CYP1A2 substrate) AUC by 3.1-fold and C_{max} by 1.3-fold *[see Drug Interactions (7.1)]*.

Effect of givosiran on CYP2D6 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased dextromethorphan (sensitive CYP2D6 substrate) AUC by 2.4-fold and C_{max} by 2.0-fold *[see Drug Interactions (7.1)]*.

Effect of givosiran on other CYP450 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased losartan (CYP2C9 substrate) AUC by 1.1-fold with no change in C_{max}; increased omeprazole (sensitive CYP2C19 substrate) AUC by 1.6-fold and C_{max} by 1.1-fold; increased midazolam (sensitive CYP3A4 substrate) AUC by 1.5-fold and C_{max} by 1.2-fold. These changes in exposure were not considered clinically relevant.

In Vitro Studies

Effect of givosiran on CYP450 Enzymes: In vitro studies indicate that givosiran does not directly inhibit or induce CYP enzymes; however, because of its pharmacological effects on the hepatic heme biosynthesis pathway, givosiran has the potential to reduce the activity of CYP enzymes in the liver.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in Sprague Dawley rats administered 25, 50, or 100 mg/kg givosiran by subcutaneous injection every 28 days for up to 89 weeks (males) or 85 weeks (females), givosiran doses in rats were 2, 3, and 6 times, respectively, the MRHD based on body surface area. A statistically significant increase in hepatocellular adenomas occurred in males at 100 mg/kg/month, the clinical significance of which is uncertain.

In a carcinogenicity study in male and female Tg.rasH2 mice administered givosiran by subcutaneous injection every 28 days for 26 weeks, up to 1500 mg/kg, givosiran was not carcinogenic.

Givosiran was not genotoxic in the in vitro bacterial reverse mutation (Ames) assays, an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes or the in vivo micronucleus assay in rats.

In fertility and early embryonic development studies, givosiran administered subcutaneously once weekly at doses up to 30 mg/kg in male and female rats prior to and during mating, and continuing in females throughout organogenesis, resulted in no adverse effects on fertility or reproductive function in male or female animals.

14 CLINICAL STUDIES

The efficacy of GIVLAARI in patients with acute hepatic porphyria was evaluated in the ENVISION trial (NCT03338816), a randomized, double-blind, placebo-controlled, multinational study.

ENVISION enrolled 94 patients with acute hepatic porphyria (AHP) (89 patients with AIP, 2 patients with variegate porphyria [VP], 1 patient with hereditary coproporphyria [HCP], and 2 patients with no identified mutation). Eligible patients were randomized 1:1 to receive once monthly subcutaneous injections of GIVLAARI 2.5 mg/kg or placebo during the 6-month double-blind period. In this study, inclusion criteria specified a minimum of 2 porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous

hemin administration at home in the 6 months prior to study entry. After the 6-month treatment period patients were enrolled in an open label extension period for up to 30 months. Ninety-three patients were enrolled in the open label extension period. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

The median age of patients studied was 37.5 years (range 19 to 65 years), 89% of patients were female, and 78% were white. GIVLAARI and placebo arms were balanced with respect to historical porphyria attack rate, hemin prophylaxis prior to study entry, use of opioid medications, and patient-reported measures of pain symptoms between attacks.

Efficacy in the 6-month double-blind period was measured by the rate of porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration at home.

Efficacy results for GIVLAARI are provided in Table 3. On average, AHP patients on GIVLAARI experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo.

Table 3. Rate of Porphyria Attacks[a] and Days of Hemin Use in Patients with AHP Over the 6-Month Double-blind Period of ENVISION

	Patients with AHP	
	GIVLAARI (N=48)	**Placebo (N=46)**
Mean Rate (95% CI) of Porphyria Attacks	1.9 (1.3, 2.8)	6.5 (4.5, 9.3)
Rate Ratio[b] (95% CI) (GIVLAARI/placebo)	0.3[c] (0.2, 0.4)	
Mean Days (95% CI) of Hemin Use	4.7 (2.8, 7.9)	12.8 (7.6, 21.4)
Ratio[b] (95% CI) (GIVLAARI/placebo)	0.3[d] (0.1, 0.5)	

[a] Attacks that require hospitalization, urgent healthcare visits, or intravenous hemin administration at home.
[b] Adjusted for prior hemin prophylaxis status and historical attack rates. A ratio <1 represents a favorable outcome for GIVLAARI.
[c] $p < 0.0001$
[d] $p = 0.0002$

GIVLAARI also resulted in a reduction in hemin use, urinary ALA, and urinary PBG.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

GIVLAARI (givosiran) is a clear, colorless-to-yellow ready-to-use solution available in single-dose vials of 189 mg/mL in cartons containing one vial (NDC 71336-1001-1).

16.2 Storage and Handling

Store at 2°C to 25°C (36°F to 77°F).

Store GIVLAARI in its original container until ready for use.

17 PATIENT COUNSELING INFORMATION

Advise patients of the potential risks of GIVLAARI treatment:

- **Anaphylactic Reaction:** Inform patients about the risk and possible symptoms of severe hypersensitivity reactions that could occur *[see Warnings and Precautions (5.1)]*.

- **Hepatic Toxicity:** Inform patients that transaminase elevations may occur, and that laboratory testing will be conducted in the first 6 months of treatment and as clinically indicated thereafter *[see Warnings and Precautions (5.2)]*.
- **Renal Toxicity:** Inform patients that increases in serum creatinine and decreases in eGFR have been reported and that laboratory testing will be conducted as clinically indicated *[see Warnings and Precautions (5.3)]*.
- **Injection Site Reactions:** Inform patients of the signs and symptoms of injection site reactions (examples include redness, pain, itching, rash, discoloration, or localized swelling) *[see Warnings and Precautions (5.4)].*
- **Blood Homocysteine Increased**: Inform patients that increases in blood homocysteine levels have been reported when using GIVLAARI, and that laboratory testing will be conducted prior to and during treatment with GIVLAARI. Vitamin supplementation may be considered for elevated blood homocysteine levels *[see Warnings and Precautions (5.5)].*

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