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

BILLING AND CODING GUIDE

Physician Office

Coverage, coding, and payment in the physician office[a]

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

Coverage

- **For Medicare patients** receiving GIVLAARI who are covered under Medicare Part B, the Medicare Administrative Contractors (MACs) may require additional documentation to determine the medical necessity of the treatment, although prior authorization is not required[a,b]
- **For patients enrolled in a State Medicaid or commercial health plan**, GIVLAARI coverage will vary by payer

Payment

Payer Type	Payment Methodology
Medicare Fee-for-Service	Average Sales Price (ASP) + 6%[c]
State Medicaid and Commercial Payers	Payment rates will vary by payer and provider contract

[a]It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact third-party payers for specific information on their coding, coverage, and payment policies.
[b]Medicare Advantage Plans may require a prior authorization for GIVLAARI.
[c]Does not account for any required payment reductions if sequestration is in effect.

Alnylam **Field Reimbursement Directors** are available to meet with you and your staff to answer coverage, coding and reimbursement questions about GIVLAARI. Contact Alnylam Assist® at 1-833-256-2748.

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

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

Coding[a]

Please refer to the table below to support appropriate claims submission for GIVLAARI® (givosiran).

Code Type	Code	Code Description
ICD-10-CM	E80.20 E80.21 E80.29	Unspecified porphyria Acute intermittent (hepatic) porphyria Other porphyria
CPT®[b]	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	J0223	Injection, givosiran, 0.5 mg
NDC	10-digit: 71336-1001-1 11-digit: 71336-1001-01	189 mg/mL single-dose vial

[a]It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact payers for specific information on their coding, coverage, and payment policies.

[b]CPT Copyright 2019 American Medical Association. All rights reserved.

CPT® is a registered trademark of the American Medical Association.

Applicable FARS/DFARS Restrictions Apply to Government Use.

Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; CPT=Current Procedural Terminology; HCPCS=Healthcare Common Procedure Coding System; NDC=National Drug Code.

Providers should consult the ICD-10-CM code book and use their own clinical judgment to confirm coding.

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

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

Physician office: sample CMS-1500 claim form

GIVLAARI® (givosiran) and the associated services provided in a physician office are billed on the CMS-1500 claim form or its electronic equivalent. A sample CMS-1500 claim form for billing GIVLAARI is provided on the next page.

- The following CMS-1500 claim form for GIVLAARI is for illustrative purposes
- It is the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for the products and services rendered
- Providers should contact payers for specific information on their coding, coverage, and payment policies
- Payers may limit the charges on a single claim, rejecting claims over the specified limit. Providers should contact payers for information on claim charge limits and claims submission guidance
- Medicare claims require the use of the JW (drug amount discarded/not administered to any patient) or JZ (zero drug amount discarded/not administered to any patient) modifiers when applicable
  - Effective for dates of service on or after January 1, 2017, Medicare requires the use of the JW modifier on any claims for single-use vials when there is discarded drug
  - Effective for dates of service on or after July 1, 2023, Medicare requires the use of the new JZ modifier on any claims for single-use vials when there are no discarded drug amount
  - Wastage-reporting policies for payers other than Medicare may vary. Providers should check with their specific plans about policies related to billing for discarded drug and use of the JW and JZ modifier
- Providers should contact their billing software vendors to ensure that they are utilizing the recommended loops and segments

Dosing calculation example

- GIVLAARI is supplied as a 189 mg/mL solution in a single-dose vial
- The recommended dose of GIVLAARI is 2.5 mg/kg administered via subcutaneous injection once monthly
- Dosing is based on actual body weight

Calculation

How to Calculate Dosage (mg)	How to Calculate Injection Volume (mL)
(body weight [kg] x 2.5 mg/kg) = mg	(mg x 1 mL/189 mg) = mL

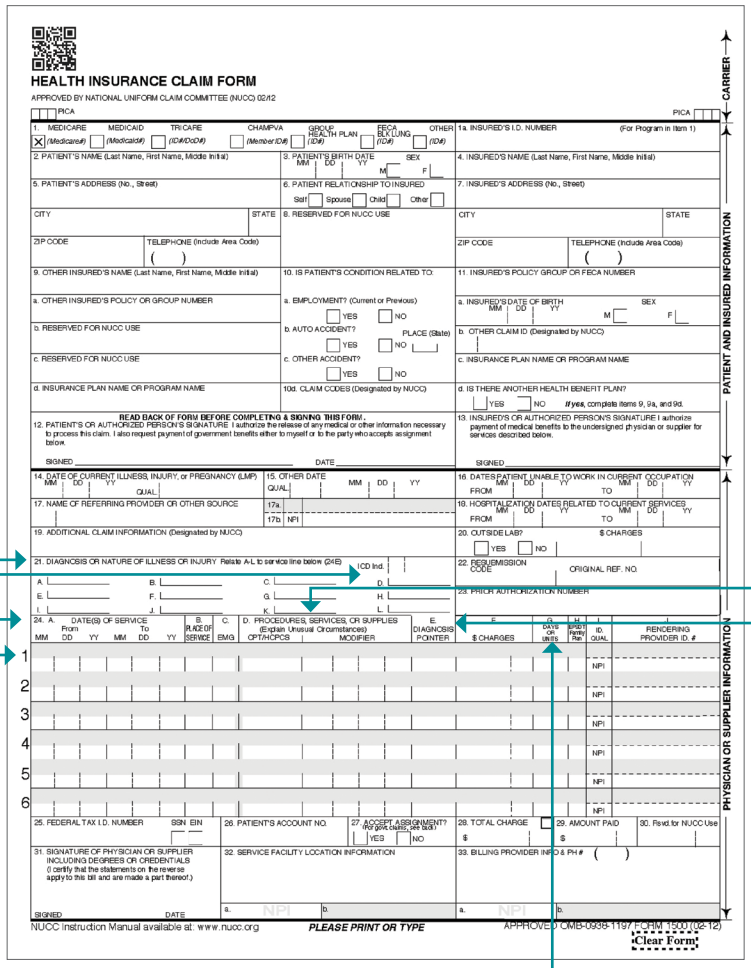
Example - 68 kg patient

Dosage (mg)	Injection Volume (mL)
68 kg x 2.5 mg/kg = 170 mg	170 mg x 1 mL/189 mg = 0.9 mL

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

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

Sample CMS-1500 Claim Form


HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) MEDICAID (Medicaid#) TRICARE (ID#/DoD#) CHAMPVA (Member ID#) GROUP HEALTH PLAN (ID#) FECA BLK LUNG (ID#) OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self Spouse Child Other

7. INSURED'S ADDRESS (No., Street)

CITY STATE

8. RESERVED FOR NUCC USE

CITY STATE

ZIP CODE TELEPHONE (Include Area Code) ( )

ZIP CODE TELEPHONE (Include Area Code) ( )

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? YES NO PLACE (State)

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO If yes, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.

15. OTHER DATE QUAL. MM DD YY

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM TO

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE

17a.

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM TO

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. B. C. D.

E. F. G. H.

I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY To MM DD YY | B. PLACE OF SERVICE | C. EMG | D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS MODIFIER | E. DIAGNOSIS POINTER | F. $ CHARGES | G. DAYS OR UNITS | H. EPSDT Family Plan | I. ID. QUAL. | J. RENDERING PROVIDER ID. #

1 NPI

2 NPI

3 NPI

4 NPI

5 NPI

6 NPI

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

Clear Form

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

LOCATOR
21
Enter the appropriate primary diagnosis code from the patient's medical record in Locator 21A.

LOCATOR
21 ICD-IND
Enter "0" to indicate use of ICD-10-CM diagnosis coding system.

LOCATOR
24A-B
Enter the date of service and the appropriate place of service code.

LOCATOR
24
Enter the GIVLAARI® (givosiran) HCPCS code J0223 on the first line and the CPT code 96372 for drug administration on the second line.

LOCATOR
24D
Enter the appropriate HCPCS code for GIVLAARI: J0223 (injection, givosiran, 0.5 mg).

Shaded area of Locator 24D (when applicable): N4713361000101 MLX (X = number of ML; for example, ML1 = 1 vial, ML2 = 2 vials, etc.)

LOCATOR
24E
Specify the diagnosis, from Locator 21, that relates to the product or procedure listed in Locator 24D.

LOCATOR
24G
Enter the number of service units for each line item.

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

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

Clean claim filing checklist

- **Select the appropriate primary diagnosis**
- **Confirm appropriate clinical documentation to support diagnosis**
- **Understand any payer-specific requirements (prior authorization, coding details, etc.)**
- **Utilize all appropriate ICD-10, CPT®, and HCPCS codes**
  - For all claims in the physician office setting, use HCPCS J0223 (Injection, givosiran, 0.5 mg)[a]
    - Remember: Billing Unit = 0.5 mg
  - Remember to use the sample claim form on page 5 as a guide
- **Anticipate requests from payers for additional clinical information prior to claims being processed for payment**

It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for those products and services rendered. Contact third-party payers for specific information on their coding and payment policies.

[a]HCPCS codes for GIVLAARI® (givosiran) may vary for dates of service prior to July 1, 2020.

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

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

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).

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.

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

Alnylam ASSIST®

Monday–Friday, 8AM–6PM

: 1-833-256-2748 | : 1-833-256-2747

To learn more about GIVLAARI® (givosiran), visit GIVLAARIHCP.com.

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

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

Alnylam® PHARMACEUTICALS

AS1-USA-01615

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*

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*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.

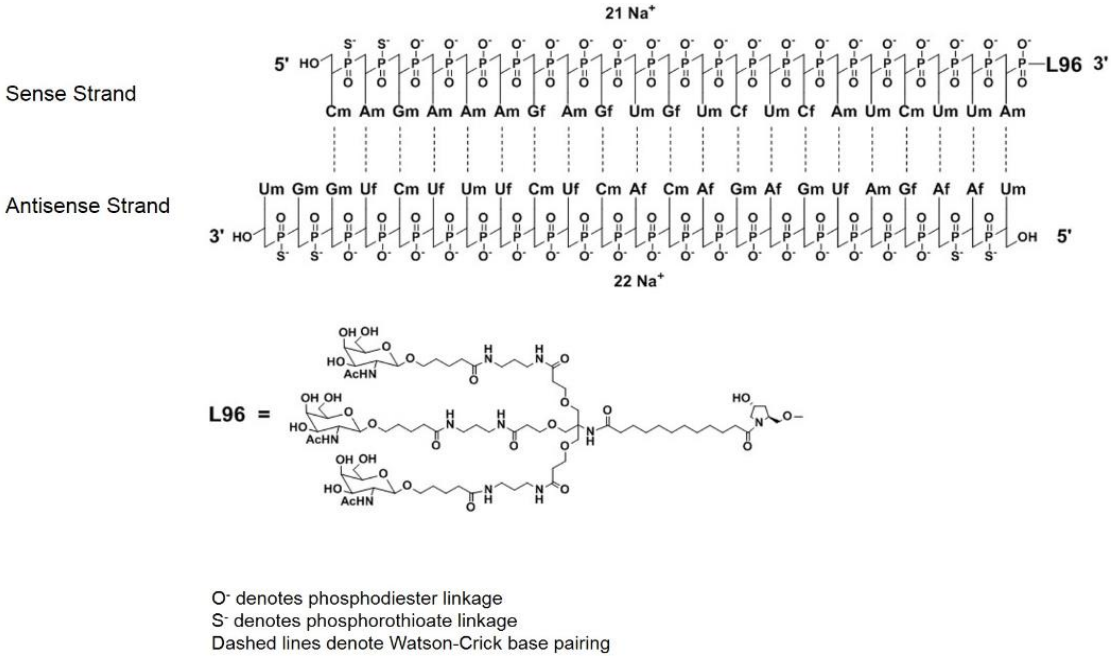
8.5 Geriatric Use

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)].*

Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142
Manufactured by: Ajinomoto Althea, Inc., 11049 Roselle Street, San Diego, CA 92121

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