For adults with acute hepatic porphyria (AHP), including acute intermittent porphyria (AIP),

GIVLAARI® (givosiran)
SIGNIFICANTLY REDUCED ATTACKS\(^1,2\)

During the 6-month double-blind period of the ENVISION trial, patients with AHP experienced 70% fewer attacks on average with GIVLAARI vs placebo\(^1\)

Attacks were defined as those requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.\(^1\)

For more information about the ENVISION trial, please see page 6.

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

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

Please see Important Safety Information on page 21 and full Prescribing Information.
AHP is a rare, genetic disease characterized by debilitating, potentially life-threatening attacks\(^2,3\)

There are 4 types of AHP\(^2,4\)

- **Acute Intermittent Porphyria (AIP)**
  \(~80\% of all AHP cases are AIP\(^2\)

- **Variegate Porphyria (VP)**

- **Hereditary Coproporphyria (HCP)**

- **ALAD-Deficiency Porphyria (ADP)**

**AHP attacks can be unpredictable, severe, and progressive\(^2\)**

- AHP is most commonly seen in women of childbearing age\(^4\)
- Attacks generally last 3 to 7 days, but recovery can take longer\(^2,5\)
- Severe attacks may progress to respiratory failure or paralysis, leading to temporary or permanent disability\(^3,5\)
- Some patients with AHP may develop long-term complications, such as chronic kidney disease (CKD), hepatocellular carcinoma (HCC), and hypertension\(^5\)
Common signs and symptoms of an AHP attack\textsuperscript{3,6,7}

Severe, diffuse abdominal pain\textsuperscript{6,7} +

1 or more of the following

**AUTONOMIC Nervous System\textsuperscript{6,7}**
- Nausea/vomiting
- Constipation
- Tachycardia
- Systemic arterial hypertension

**CENTRAL Nervous System\textsuperscript{3,6,7}**
- Seizures
- Anxiety
- Mental status changes

**PERIPHERAL Nervous System\textsuperscript{6,7}**
- Limb weakness or pain
- Peripheral neuropathy

**CUTANEOUS\textsuperscript{7}**
- Skin lesions on sun-exposed areas
  (Cutaneous symptoms primarily occur in HCP and VP.)

**OTHER Common AHP Symptoms\textsuperscript{7,8}**
- Hyponatremia
- Dark, reddish urine

\textsuperscript{AHP=acute hepatic porphyria; HCP=hereditary coproporphyria; VP=variegate porphyria.}

>90% of patients report abdominal pain during AHP attacks\textsuperscript{6}
Patients with AHP have an enzyme deficiency in the heme biosynthesis pathway. ALAS1 upregulation leads to accumulation of neurotoxic intermediates that can cause damage across the body.

Disease triggers, such as infections or certain medications, can induce ALAS1 and lead to overproduction of the neurotoxic intermediates ALA and PBG.

ALA and PBG accumulate in the liver, and are further released into circulation, thereby causing neurotoxic effects.

Neurotoxic effects can lead to acute attacks.

Neurotoxic intermediates ALA and PBG are factors associated with AHP attacks and other disease manifestations.
GIVLAARI® (givosiran) specifically targets ALAS1, key to the pathophysiology of AHP

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

GIVLAARI targets ALAS1 mRNA for degradation, thereby reducing the production of the neurotoxic intermediates ALA and PBG

Less ALA and PBG are released into circulation

Reductions of ALA and PBG have been associated with fewer attacks

AHP=acute hepatic porphyria; ALA=aminolevulinic acid; ALAS1=aminolevulinic acid synthase 1; mRNA=messenger RNA; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

Anaphylactic Reaction

Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

Please see Important Safety Information on page 21 and full Prescribing Information.
ENVISION study design

ENVISION is a randomized, double-blind, placebo-controlled, multinational phase 3 study in adult patients with AHP (N=94), with a 30-month open-label extension (OLE) period (N=93)^1,13,14

**Key Inclusion Criteria**
- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks within prior 6 months
- Wiling to discontinue and/or not initiate hemin prophylaxis

**1:1 Randomization (N=94)**

**Primary Efficacy Measure**
- Rate of AHP attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home

**Additional Efficacy Measures**
- ALA and PBG levels
- Hemin use
- Daily worst pain*
- Analgesic use*

**6-Month Double-Blind Period**

| GIVLAARI (N=48) SC qM 2.5 mg/kg | OR | Placebo (N=46) SC qM |

| GIVLAARI (N=56) SC qM 2.3 mg/kg |

**30-Month OLE Period†**

| GIVLAARI (N=93) SC qM 2.5 mg/kg |

| GIVLAARI (N=37) SC qM 1.25 mg/kg |

• Patients who experienced an AHP attack were treated according to the local standard of care, which could include IV hemin^13

**ENVISION is the largest interventional study in AHP^1,14**

---

^1 These measures were in patients with AIP only.

^2 All endpoints were considered exploratory in the ENVISION OLE period.

^3 A protocol amendment increased the dose for all patients to 2.5 mg/kg once monthly.

---

AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; PBG=porphobilinogen; qM=once monthly; SC=subcutaneous.

### IMPORTANT SAFETY INFORMATION

#### Hepatic Toxicity

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

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

*Please see Important Safety Information on page 21 and full Prescribing Information.*
## ENVISION study patient population\(^1,\)\(^13\)

<table>
<thead>
<tr>
<th>Baseline Demographic and Clinical Characteristics of Patients With AHP(^13)</th>
<th>GIVLAARI(^\circledast) (givosiran) (N=48)</th>
<th>Placebo (N=46)</th>
<th>Overall (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>42 (19, 65)</td>
<td>36 (20, 60)</td>
<td>37.5 (19, 65)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>43 (90)</td>
<td>41 (89)</td>
<td>84 (89)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>39 (81)</td>
<td>34 (74)</td>
<td>73 (78)</td>
</tr>
<tr>
<td>AHP type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– AIP</td>
<td>46 (96)</td>
<td>43 (93)</td>
<td>89 (95)</td>
</tr>
<tr>
<td>– HCP</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>– VP</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>– No identified mutation</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Historical annualized attack rate, median [IQR]</td>
<td>8 [4-18]</td>
<td>7 [4-14]</td>
<td>8 [4-16]</td>
</tr>
<tr>
<td>Prior hemin prophylaxis, n (%)</td>
<td>20 (42)</td>
<td>18 (39)</td>
<td>38 (40)</td>
</tr>
<tr>
<td>Prior chronic opioid use, n (%)(^6)</td>
<td>14 (29)</td>
<td>13 (28)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Prior chronic symptoms, n (%)(^7)</td>
<td>23 (48)</td>
<td>26 (57)</td>
<td>49 (52)</td>
</tr>
</tbody>
</table>

\(^6\)Use of opioids was defined as chronic if patients reported taking them for porphyria daily, or on most days, when not having an attack.\(^14\)

\(^7\)Symptoms were chronic if patients experienced symptoms of porphyria daily, or on most days, when not having an attack.\(^14\)

The historical annualized attack rate was calculated as the number of attacks resulting in a composite of hospitalization, a visit to a health care facility, or hemin use at home during the 6 months before randomization.\(^13\)

---

All eligible patients (93 of 94) enrolled in the open-label extension\(^14\)

---

<table>
<thead>
<tr>
<th>IMPORTANT SAFETY INFORMATION</th>
</tr>
</thead>
</table>

**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.

Please see Important Safety Information on page 21 and full Prescribing Information.
Treatment with GIVLAARI® (givosiran) resulted in rapid and sustained reductions in ALA and PBG¹

Reductions through the ENVISION 6-month double-blind period¹,¹³

- Reductions in urinary ALA and PBG were seen with GIVLAARI 2.5 mg/kg at Day 14, the first time point measured
  - 14 days after the first dose of GIVLAARI, median reductions from baseline in urinary ALA and PBG were 84% and 75%, respectively
- Maximal reductions in ALA and PBG levels were achieved around Month 3 with GIVLAARI 2.5 mg/kg, with median reductions from baseline of 94% for ALA and 95% for PBG, and were sustained thereafter with repeated once-monthly dosing

Reductions in the ongoing ENVISION open-label extension (OLE) period¹³⁻¹⁵

- In patients who continued treatment with GIVLAARI in the OLE period, reductions in urinary ALA and PBG were sustained through Month 24
  - 89.5% median reduction (Q1, Q3: 94.0%, 80.4%) and 91.1% median reduction (Q1, Q3: 96.7%, 75.1%) from baseline in urinary ALA and PBG, respectively
- In patients who crossed over from placebo to GIVLAARI in the OLE period (a total of 18 months of treatment with GIVLAARI):
  - 89.3% median reduction (Q1, Q3: 94.2%, 81.3%) and 93.5% median reduction (Q1, Q3: 96.4%, 66.5%) from baseline in urinary ALA and PBG, respectively, was observed at Month 24

ALA=aminolevulinic acid; PBG=porphobilinogen.

IMPORTANT SAFETY INFORMATION

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

Please see Important Safety Information on page 21 and full Prescribing Information.
In a 24-month interim analysis of patients with AHP in the ENVISION OLE, Sustained reductions in ALA and PBG continued with treatment of GIVLAARI® (givosiran)\(^{14}\)

**Urinary ALA levels\(^{14}\)**

**Urinary PBG levels\(^{14}\)**

**IMPORTANT SAFETY INFORMATION**

**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).

*The determination of the ULN for ALA (1.5 mmol/mol of creatinine) was based on samples obtained from 150 healthy persons.

\(^{1}\)Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.

\(^{2}\)The determination of the ULN for PBG (0.14 mmol/mol of creatinine) was based on samples obtained from 150 healthy persons.

AHP=acute hepatic porphyria; ALA=aminolevulinic acid; DB=double-blind; OLE=open-label extension; PBG=porphobilinogen; ULN=upper limit of normal.

Please see Important Safety Information on page 21 and full Prescribing Information.
In patients with AHP in the ENVISION 6-month double-blind period, treatment with GIVLAARI® (givosiran) led to a significant reduction in porphyria attacks\(^1\)

- Attack rate ratio of GIVLAARI vs placebo: 0.3 (95% CI: 0.2, 0.4; \(P<0.0001\))\(^1\)

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.\(^1\)

AHP=acute hepatic porphyria; CI=confidence interval.

**IMPORTANT SAFETY INFORMATION**

**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.

Please see Important Safety Information on page 21 and full Prescribing Information.
**In a 24-month analysis of patients with AHP in the ENVISION OLE, Patients continuing treatment with GIVLAARI® (givosiran) had sustained attack reduction**¹⁴,¹⁶

**Average number of attacks per 3-month interval**¹⁶

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GIVLAARI (N)</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>47</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>Crossover (Placebo to GIVLAARI) (N)</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>45</td>
<td>45</td>
<td>44</td>
<td>43</td>
<td>42</td>
<td>41</td>
<td>18</td>
</tr>
</tbody>
</table>

*Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.*¹⁴

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.¹⁴

- Attack reduction was sustained in patients continuing treatment with GIVLAARI during the ENVISION OLE period¹⁴,¹⁶
- Patients who crossed over from placebo to GIVLAARI had attack reduction in the OLE period (for a total of 18 months of treatment) similar to that seen in GIVLAARI patients in the double-blind period¹³
- Endpoints in the OLE period are exploratory¹⁷

AHP=acute hepatic porphyria; DB=double-blind; OLE=open-label extension.

**IMPORTANT SAFETY INFORMATION**

**Adverse Reactions**

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

Please see Important Safety Information on page 21 and full Prescribing Information.
In patients with AHP in the ENVISION 6-month double-blind period, a greater number of patients treated with GIVLAARI® (givosiran) had zero attacks vs placebo\textsuperscript{13}

**50% of patients** receiving attack-preventive treatment with GIVLAARI had zero attacks in the 6-month DB period vs 17% of placebo patients\textsuperscript{13}

Attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.\textsuperscript{1}

AHP=acute hepatic porphyria; DB=double-blind.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

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

Please see Important Safety Information on page 21 and full Prescribing Information.
In a 24-month interim analysis of patients with AHP in the ENVISION OLE, The number of patients with zero attacks increased with continued attack-preventive treatment with GIVLAARI® (givosiran)\(^{14}\)

**Proportion of attack-free\(^*\) patients by 3-month\(^{†}\) intervals during DB and OLE periods\(^{14}\)**

![Graph showing proportion of attack-free patients by 3-month intervals during DB and OLE periods.]

- **Endpoints in the OLE period are exploratory\(^{17}\)**

\(^a\)Attacks were defined as those that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.\(^{14}\)

\(^{†}\)1 month = 28 days.\(^{14}\)

\(^{†}\)Data for GIVLAARI 1.25 mg/kg and 2.5 mg/kg in the OLE period were pooled.\(^{14}\)

\(^{§}\)Baseline represents 6 months before randomization.\(^{14}\)

**IMPORTANT SAFETY INFORMATION**

**Anaphylactic Reaction**
Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

**Please see Important Safety Information on page 21 and full Prescribing Information.**
Significantly less hemin was used by patients treated with GIVLAARI® (givosiran)\(^1\)

In patients with AHP in the ENVISION 6-month double-blind (DB) period

12.8

-70%

4.7

70% reduction in average days of hemin use with GIVLAARI vs placebo\(^1\)

- Ratio of average days of hemin use (GIVLAARI:placebo): 0.3 (95% CI: 0.1, 0.5; \(P=0.0002\))\(^1\)

- In the ENVISION 6-month DB period, 54% of patients with AIP (n=25/46) treated with GIVLAARI had zero days of hemin use compared with 23% of patients (n=10/43) receiving placebo\(^1\)

**Hematom Use**

- Average Days of Hemin Use

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=46)</th>
<th>GIVLAARI 2.5 mg/kg (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12.8</td>
<td>4.7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(95% CI: 7.6, 21.4)</td>
<td>95% CI: 2.8, 7.9)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION**

**Hepatic Toxicity**

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

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

Please see Important Safety Information on page 21 and full Prescribing Information.
In a 24-month interim analysis of patients with AHP in the ENVISION OLE, more patients had zero days of hemin use with GIVLAARI® (givosiran) treatment.

**Patients who continued GIVLAARI treatment**

- **GIVLAARI 2.5 mg/kg (N=48)**
  - DB period (0-6 months): 54.2%
  - OLE period (>6 months): 68.1%

**Patients who crossed over from placebo to GIVLAARI**

- **Placebo (N=46)**
  - 26.1%
- **GIVLAARI 2.5 mg/kg (N=48)**
  - DB period (0-6 months): 48.9%
  - OLE period (>6 months):

Endpoints in the OLE period are exploratory.

AHP=acute hepatic porphyria; DB=double-blind; OLE=open-label extension.

**IMPORTANT SAFETY INFORMATION**

**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.

Please see Important Safety Information on page 21 and full Prescribing Information.
Daily worst pain in the ENVISION 6-month double-blind period

Daily worst pain score in patients with AIP was a secondary endpoint

- Pain was measured using patient-reported daily worst pain scores based on a numeric rating scale (NRS)
- A statistical analysis of the change from baseline in daily worst pain score for GIVLAARI® (givosiran) vs placebo was conducted
- A positive score represents a worsening in daily worst pain from baseline; a negative score represents an improvement from baseline
- GIVLAARI did not meet statistical significance for this endpoint based on the prespecified statistical method
- The daily worst pain scores were lower with GIVLAARI compared with placebo

| Daily worst pain scores in patients with AIP (AUC of mean change from baseline) |
|-------------------------------|-------------------------------|-------------------------------|
| **GIVLAARI** (N=46) (95% CI)  | **Placebo** (N=43) (95% CI)   | **Treatment difference** (95% CI) |
| -12.876 (-21.776, -3.976)     | -0.196 (-9.468, 9.077)        | -12.680 (-25.526, 0.166)        |

AIP=acute intermittent porphyria; AUC=area under the curve; CI=confidence interval.

**IMPORTANT SAFETY INFORMATION**

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

Please see Important Safety Information on page 21 and full Prescribing Information.
Analgesic use in patients with AIP in the ENVISION 6-month double-blind period\textsuperscript{13}

**Analgesic use in patients with AIP was a prespecified exploratory endpoint\textsuperscript{13}**

- Through Month 6, the proportion of days with opioid and nonopioid analgesic use was lower in patients treated with GIVLAARI\textsuperscript{®} (givosiran) compared with placebo\textsuperscript{13}
- An evaluation compared with baseline analgesic use cannot be conducted because the proportion of days with analgesic use was not captured at baseline\textsuperscript{13}

![Analgesic Use Graph](image)

AIP=acute intermittent porphyria.

**IMPORTANT SAFETY INFORMATION**

**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).

Please see Important Safety Information on page 21 and full Prescribing Information.
Safety profile of GIVLAARI® (givosiran) in the ENVISION study

Safety during the 6-month DB period

Adverse reactions that occurred at least 5% more frequently in patients treated with GIVLAARI compared with patients receiving placebo in the 6-month double-blind (DB) period

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>GIVLAARI (N=48) n (%)</th>
<th>Placebo (N=46) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>13 (27)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>12 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Rasha</td>
<td>8 (17)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Serum creatinine increaseb</td>
<td>7 (15)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Transaminase elevations</td>
<td>6 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

a Grouped term includes pruritus, eczema, erythema, rash, rash pruritic, urticaria.
b Grouped term includes blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease (decreased eGFR).

- Permanent discontinuation of GIVLAARI occurred in 1 patient (2.1%) due to elevated transaminases, in adherence with prespecified protocol-defined stopping rules
- The most frequently occurring (≥20% incidence) adverse reactions reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%)

Safety during the open-label extension (OLE) period

- The most frequently occurring (≥20%) adverse reactions reported in patients treated with GIVLAARI were injection-site reactions (37%), nausea (34%), fatigue (23%), nasopharyngitis (23%), and headache (20%)
- Serious adverse events were reported in 28 (30%) of patients during the study. SAEs reported in more than 1 patient included blood homocysteine increased, CKD, device breakage, pyrexia, and urinary tract infections (all reported in 2 patients)
- Three patients discontinued treatment due to adverse events in the OLE period. One patient discontinued treatment due to an AE of hypersensitivity, and two patients discontinued due to SAEs of increased blood homocysteine
- Increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI

AE=adverse event; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; SAE=serious adverse event.

IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on page 21 and full Prescribing Information.
Once-monthly dosing with GIVLAARI® (givosiran)\(^1\)

The recommended dose of GIVLAARI is 2.5 mg/kg administered via subcutaneous injection once monthly by a healthcare professional. Dosing is based on actual body weight.\(^1\)

**Missed dose**

- Administer GIVLAARI as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose\(^1\)

**Dose modifications 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\(^1\)

- In patients who resume dosing at 1.25 mg/kg once monthly without recurrence of severe or clinically significant transaminase elevations, the dose may be increased to the recommended 2.5 mg/kg once monthly\(^1\)

**GIVLAARI is administered via subcutaneous injection by a healthcare professional only\(^1\)**

- Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI\(^1\)

---

For detailed instructions on the administration of GIVLAARI, see the full Prescribing Information

---

**IMPORTANT SAFETY INFORMATION**

**Injection Site Reactions**

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

Please see Important Safety Information on page 21 and full Prescribing Information.
Alnylam Assist® provides personalized support for patients

Alnylam Assist® is here to help your patients:

- Get started on treatment with GIVLAARI® (givosiran)
- Understand their benefits and coverage, including financial assistance options for eligible patients*
- Learn more about acute hepatic porphyria and treatment with GIVLAARI

Monday-Friday, 8 AM–6 PM ET

1-833-256-2748
1-833-256-2747

To learn more, visit www.AlnylamAssist.com

How to get started:

1. Complete Start Form
2. Alnylam Case Manager Reaches Out
3. Patient Assistance Offered

After discussing GIVLAARI with your patient, begin the enrollment process by completing the GIVLAARI Start Form. Upon receipt of the Start Form, an Alnylam Case Manager dedicated to your patient’s needs will reach out to you and your patient within 2 business days.

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

Please see Important Safety Information on page 21 and full Prescribing Information.
Indication and Important Safety Information

**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

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

Anaphylactic Reaction
Anaphylaxis has occurred with GVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GVLAARI 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 GVLAARI 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 GVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GVLAARI 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 GVLAARI. In the placebo-controlled study, 15% of patients receiving GVLAARI experienced a renal-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GVLAARI as clinically indicated.

Injection Site Reactions
Injection site reactions were reported in 25% of patients receiving GVLAARI 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 GVLAARI. 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 GVLAARI. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

Drug Interactions
Concomitant use of GVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GVLAARI 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 GVLAARI were nausea (27%) and injection site reactions (25%).

For additional information about GVLAARI, please see full Prescribing Information.
GIVLAARI® (givosiran)

SIGNIFICANTLY REDUCED ATTACKS
in adults with acute hepatic porphyria (AHP)¹

GIVLAARI is an RNA interference (RNAi) therapeutic that targets ALAS1 mRNA in the liver, leading to reductions in levels of ALA and PBG, factors associated with AHP attacks and other disease manifestations.² ¹

Efficacy findings from the ENVISION 6-month DB period and ongoing OLE period
- 70% fewer porphyria attacks on average with GIVLAARI vs placebo in the 6-month DB period of ENVISION¹
- Attack reduction was sustained for patients continuing to receive GIVLAARI through Month 24 of the OLE period.¹¹

Attacks were defined as those requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home.¹

Safety findings from the ENVISION 6-month DB period and ongoing OLE period
- During the 6-month DB period, permanent discontinuation of GIVLAARI occurred in 1 patient (2.1%) due to elevated transaminases, in adherence with prespecified protocol-defined stopping rules.¹
- The most common adverse reactions (≥20%) reported in patients treated with GIVLAARI were nausea (27%) and injection site reactions (25%) in the 6-month DB period.¹
- Three patients discontinued treatment due to adverse events in the OLE period. One patient discontinued treatment due to an AE of hypersensitivity, and two patients discontinued due to SAEs of increased blood homocysteine.¹⁴ ¹⁹
- The most frequently occurring (≥20%) adverse reactions reported in patients treated with GIVLAARI were injection-site reactions (37%), nausea (34%), fatigue (23%), nasopharyngitis (23%), and headache (20%) in the OLE period.¹⁴
- In the OLE period of the ENVISION study, increased blood homocysteine was reported in 15 of 93 (16%) patients treated with GIVLAARI.¹

ALGAIR® and Alnylam Assist are registered trademarks of Alnylam Pharmaceuticals, Inc. © 2022 Alnylam Pharmaceuticals, Inc. All rights reserved. AS1-USA-00193-V4

Please see Important Safety Information on page 21 and full Prescribing Information.