WellMed Doctors helping patients for more than 25 years	**Effective Date: 10/27/23**	**Revision Date(s):**
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Policy Number: 065.000

Title: Coverage Determination Policy for Givlaari (givosiran)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

WellMed Coverage Determination Policies are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support WellMed coverage decision making. WellMed may modify these Policy Guidelines at any time. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the WellMed Coverage Determination Policies is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

Doctors helping patients for more than 25 years

Title: Coverage Determination Policy for Givlaari (Givosiran)

Coverage Policy Number: 065.000

Line of Business: Medicare Part B

Policy Type: Prior Authorization

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Coverage Determination:

Initial/New Requests

Givlaari (givosiran) is proven and/or medically necessary for the treatment of **Acute Hepatic Porphyrias (AHP)** when **ALL** of the following are met:

A. Diagnosis of an acute hepatic porphyria (AHP) [i.e., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, ALA dehydratase deficient porphyria]

B. **One** of the following

   I. Patient has active disease as defined in the clinical trial by having at least 2 documented porphyria attacks within the past 6 months

   II. Patient is currently receiving treatment with prophylactic hemin to prevent porphyria attacks

C. Provider attestation that the patient's baseline (before givosiran is initiated) hemin administration requirements (prophylactic or treatment) and rate and/or number of porphyria attacks has been documented

D. Patient has not had a liver transplant

E. Patient will not receive concomitant prophylactic hemin treatment while on Givlaari

F. Prescribed by, or in consultation with, a hematologist or a specialist

G. Givlaari dosing is in accordance with the United States Food and Drug Administration approved labeling

H. Initial authorization will be for no more than 6 months.

Renewal/Continuation of Therapy Requests

Givlaari (givosiran) will be approved for Renewal/Continuation of Therapy Requests when **ALL of the following are met**:

A. Patient has previously received Givlaari for the treatment of AHP

B. Documentation that the patient has experienced a positive clinical response while on Givlaari by demonstrating **ALL** of the following from pre-treatment baseline:

I. Reduction in hemin administration requirements (if previously required, including prophylactic and/or treatment doses)

II. Reduction in the rate and/or number of porphyria attacks

III. Improvement of signs and symptoms of AHPs (e.g., pain, neurological, gastrointestinal, renal, quality of life, etc.)

IV. Patient has not had a liver transplant

V. Patient will not receive concomitant prophylactic hemin treatment while on Givlaari

VI. Prescribed by, or in consultation with, a hematologist or a specialist

VII. Givlaari dosing is in accordance with the United States Food and Drug Administration approved labeling

VIII. Reauthorization will be for no more than 12 months

FDA Approved Dose and Indication

FDA Approved Indication	FDA Approved Dose
Acute Hepatic Porphyria	2.5mg/kg SubQ once monthly (based on actual body weight)

General Background

Acute hepatic porphyria refers to a family of rare genetic diseases that is caused when the heme production process in the liver does not work properly because of a genetic mutation, this process is controlled by an enzyme called aminolevulinic acid synthase 1 (ALAS1)[1]. There are four types of AHP: acute intermittent porphyria (AIP), variegate porphyria (VP), Hereditary coproporphyria (HCP), and ALAD deficiency porphyria (ADP)[1].

Although there are a variety of factors that can trigger ALAS1, some of the known triggers include hormonal fluctuations, infection, stress, use of certain medications, alcohol consumption, and fasting/low-carbohydrate diets. Activation of ALAS1, causes toxic substances like aminolevulinic acid (ALA) and porphobilinogen (PBG) to build up and release throughout the body causing severe, unexplained abdominal pain is the most common symptom, which can be accompanied by limb, back, or chest pain, nausea, vomiting, confusion, anxiety, seizures, weak limbs, constipation, diarrhea, or dark or reddish urine[1]. Long-term complications and comorbidities of AHP can include hypertension, chronic kidney disease or liver disease including hepatocellular carcinoma. Currently, the population of AHP patients with diagnosed, active disease in the U.S. and Europe is estimated to be approximately 3,000[4].

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.

Clinical Evidence

The efficacy of Givlaari was established in the Phase 3 ENVISION trial, a randomized, double-blind, placebo-controlled multicenter study in 94 patients with AHP (89 patients with acute intermittent porphyria (AIP), 2 patients with variegate porphyria [VP], 1 patient with hereditary coproporphyria [HCP], and 2 patients with no identified mutation). 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. Hemin use during the study was permitted for the treatment of acute porphyria attacks. Patients were randomized to receive Givlaari or placebo during the 6-month double-blind period. 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. The mean rate of porphyria attacks was 1.9 and 6.5 for Givlaari and placebo, respectively. This represented a 70% (95% CI: 60, 80) reduction in porphyria attacks for patients receiving Givlaari vs. placebo. The mean number of days of hemin use was 4.7 (95% CI: 2.8, 7.9) with Givlaari vs. 12.8 (95% CI: 7.6, 21.4) with placebo.

HCPCS Code

HCPCS Code	J0223: givosiran, 0.5mg
Available Dosage Form(s)	189 mg/mL single-dose vial for injection
Route of Administration	Subcutaneous, to be administered by a healthcare professional only

Acronyms

AHP = Acute hepatic porphyria

ALAS1 = Aminolevulinic acid synthase 1

PBG = Porphobilinogen

AIP = Acute intermittent porphyria

VP = Variegate porphyria

HCP = Hereditary coproporphyria

ALA = Aminolevulinic acid

ADP = ALAD deficiency porphyria

References

1. Acute Hepatic Porphyria (AHP). American Liver Foundation. March 17, 2023. Accessed on September 1, 2023. https://liverfoundation.org/liver-diseases/rare-disease/acute-hepatic-porphyria-ahp/
2. ENVISION: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP). Clinicaltrials.gov website: https://clinicaltrials.gov/ct2/show/NCT03338816?term=givosiran&cond=porphyria&draw=1&rank=5. Accessed September 01, 2023.
3. Givlaari [package insert]. Cambridge, MA:Alnylam Pharmaceuticals, Inc., February 2023
4. Sood, G.K & Anderson, K.E. Acute Intermittent Porphyria: Management. UpToDate. 2022. Accessed on September 1, 2023. https://www.uptodate.com/contents/acute-intermittent-porphyria management?search=acute%20hepatic%20porphyria&source=search_result&selectedTitle=2~115&usage_type=default&display_rank=2
5. Types of Porphyria. American Porphyria Foundation. 2023. Accessed on September 1, 2023. https://porphyriafoundation.org/for-patients/types-of-porphyria/.