Effective Date **12/15/2024**
Coverage Policy Number **IP0118**

Givosiran

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for givosiran (**Givlaari®**).

Medical Necessity Criteria

Givosiran (Givlaari) is considered medically necessary when the following are met:

Treatment of Acute Hepatic Porphyria (AHP). Individual meets **ALL** of the following criteria:

A. Age 18 years or older
B. Diagnosis of acute hepatic porphyria confirmed by documentation of **BOTH** of the following:
   i. Demonstrated clinical features associated with acute hepatic porphyria (for example, neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs)
   ii. **ONE** of the following:

a. Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal
b. Elevated urinary or plasma porphobilinogen (PBG) greater than the upper limit of normal

C. Prior to starting treatment with givosiran (Givlaari), the individual has a history of one porphyria attack in the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration
D. Medication is being prescribed by, or in consultation with, a gastroenterologist, hepatologist, medical geneticist or a physician who specializes in acute hepatic porphyria

Dosing. Up to 2.5 mg/kg administered by subcutaneous injection given no more frequently than once every 30 days.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of givosiran (Givlaari) is considered medically necessary for Acute Hepatic Porphyria (AHP) when the above medical necessity criteria are met AND there is documentation of beneficial response (for example, reduction in porphyria attacks, improvement of signs and symptoms, decrease in hemin administration).

Authorization Duration

Initial approval duration: up to 6 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

Coding

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0223	Injection, givosiran, 0.5 mg

Background

OVERVIEW
Givlaari, an aminolevulinate synthase 1-directed small interfering RNA, is indicated for the treatment of **acute hepatic porphyria** (AHP) in patients ≥ 18 years of age.[1]

Givlaari 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.[1] This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid and porphobilinogen, factors associated with attacks and other disease manifestations of AHP. In the pivotal trial, inclusion criteria specified a minimum of two 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.

Disease Overview
Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] AHPs are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP) and are characterized by acute neurovisceral symptoms with or without cutaneous manifestations.[3,4] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar; however, VP and HCP patients often develop photosensitivity. Signs and symptoms of AHP usually occur intermittently and include abdominal pain, constipation, muscle weakness, pain in the arms and legs, insomnia, emotional complications, rapid pulse, and high blood pressure. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrences may develop chronic pain.

Dosing Information
The recommended dose is 2.5 mg/kg administered by subcutaneous injection once monthly by a healthcare professional only.

Guidelines
The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for evaluation and long-term management of AHPs (2017).[5] Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination. Preventative measures should be taken to prevent attacks. Hemin therapy (e.g., Panhematin® [hemin injection for intravenous infusion]) is recommended for preventative management in AHP and treatment during acute attacks. Patients with ≥ four attacks per year are candidates for either prophylactic or "on demand" infusions. The need for ongoing prophylaxis should be assessed every 6 to 12 months. Repeated long-term treatment with hemin therapy can lead to iron overload and contribute to hepatic damage and fibrosis. Carbohydrate loading (glucose tablets or dextrose solutions) has been used in early stages of an acute attack, but there are no clear data showing a benefit. Women with AHP can develop cyclic attacks correlated with the menstrual cycle. Options to prevent these attacks include recognizing and removing exacerbating factors, a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or prophylactic hemin therapy infusions.

References

1. Givlaari™ subcutaneous injection [prescribing information]. Cambridge, MA: Alnylam; April 2024.
2. Porphyria. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://ghr.nlm.nih.gov/condition/porphyria. Accessed on October 07, 2024.
3. Wang B, Rudnick S, Cengia B, et al. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2018;3(2):193-206.
4. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepat*. 2015;3(1):17-26.
5. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

Revision Details

Type of Revision	Summary of Changes	Date

Selected Revision	No criteria changes	12/15/2024

The policy effective date is in force until updated or retired.