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Reviewed: 09/11/24

Revised: 10/15/24

Subject: Givosiran (Givlaari™)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Acute Hepatic Porphyrias (AHP) are a group of rare inherited metabolic disorders caused by the accumulation of heme precursors in hepatocytes. The accumulation of aminolevulinic acid (ALA) and porphobilinogen (PBG) cause neurovisceral attacks which can be severe and life-threatening. The most common symptoms may include abdominal pain, nausea, vomiting, weakness, and constipation that last hours to several days. Irreversible neuronal damage, paralysis, or seizures may occur and signs of the disease may include tachycardia, hypertension, and dark-colored urine. Acute attacks may be treated with intravenous heme therapy and carbohydrate loading. Certain factors may increase the risk of an attack due to increased demand for hepatic heme and should be avoided if possible (e.g., stress, certain medications, fasting, alcohol, smoking, and variation in hormone production).

There are four types of AHP: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and 5-aminolevulinic acid (ALA) dehydratase deficient porphyria (ALADP). Diagnosis of AHP includes a biochemical assessment consisting of a random urine screen for elevated ALA or PBG levels during an attack and genetic testing. Four subgroups have been described based on disease activity: asymptomatic and biochemically inactive (i.e., normal ALA and PBG levels) latent genetic mutation carriers, asymptomatic high excretors (ASHE) that are biochemically active (i.e., elevated urine ALA and PBG level greater than 4 times the upper limit of normal) but without acute attacks, sporadic attack patients with less than 4 attacks per year, and recurrent attack patients with greater than 4 attacks per year.

Givosiran is a small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes. The degradation of hepatic ALAS1 mRNA leads to a reduction of aminolevulinic acid (ALA) and porphobilinogen (PBG), the neurotoxic intermediates associated with disease manifestations of AHP. Givosiran (Givlaari) is FDA-approved for adults with acute hepatic porphyria.

The efficacy of givosiran was evaluated in a randomized, double-blind, placebo-controlled study in 94 patients with AHP for 6 months. There were 89 patients with AIP, 2 with VP, 1 with HCP and 2 with no identified mutation. Included patients had 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. Patients were also required to have an elevated urinary or plasma PBG or ALA levels within the past year. Hemin use was permitted for the treatment of acute porphyria attacks. Efficacy was assessed by the rate of porphyria attacks that required hospitalizations, urgent healthcare visit or intravenous hemin administration at home. Givosiran given as a 2.5 mg/kg once monthly subcutaneous injection reduced the mean rate of porphyria attacks as compared to placebo (1.9 vs 6.5, Rate ratio 0.3, $p<0.0001$). Givosiran also reduced the mean days of hemin use as compared to placebo (4.7 vs 12.8, $p<0.0002$). The most common adverse reactions were nausea, injection site reactions, rash, serum creatinine increase, transaminase elevation and fatigue. One patient experienced an anaphylactic reaction.

POSITION STATEMENT:

Initiation of givosiran (Givlaari™) **meets the definition of medical necessity** when:

1. The member has a diagnosis of Acute Hepatic Porphyria (includes Acute Intermittent Porphyria, Hereditary Corproporhyria, Variegate Porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria)
2. Diagnosis is confirmed by **ONE** of the following – lab documentation must be submitted:
    a. Elevated urine or plasma aminolevulinic acid (ALA) or porphobilinogen (PBG) level in the past year
    b. Presence of a genetic mutation (i.e., *HMBS, CPOX, PPOX, or ALAD*)
3. The member has evidence of active disease with **ONE** of the following – documentation must be submitted:
    a. History of at least 2 porphyria attacks in the past 6 months
    b. History of one severe attack in the past year with central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS) involvement (e.g., hallucinations, seizures, respiratory failure, paralysis)
    c. Member is currently receiving hemin for the prevention of porphyria attacks
4. Medications designated as very likely to be unsafe for individuals with Acute Hepatic Porphyria* have been discontinued when clinically appropriate
5. The medication is prescribed by, or in consultation with, a specialist in the treatment of acute hepatic porphyria (e.g., hematologist, hepatologist)
6. The dose does not exceed 2.5 mg/kg subcutaneous injection once monthly

Approval duration: 6 months

Continuation of givosiran (Givlaari™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. An authorization or reauthorization for givosiran has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of Acute Hepatic Porphyria, **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has a beneficial response to treatment (e.g., reduction in acute attacks) – documentation must be submitted
3. Medications designated as very likely to be unsafe for individuals with Acute Hepatic Porphyria* have been discontinued when clinically appropriate
4. The dose does not exceed 2.5 mg/kg subcutaneous injection once monthly

Approval duration: 12 months

*Searchable database at https://porphyriafoundation.org/drugdatabase/drug-safety-database-search/

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Adults with acute hepatic porphyria (AHP): 2.5 mg/kg subcutaneous injection once monthly by a healthcare professional (dose based on actual body weight). Divide doses requiring volumes greater than 1.5 mL equally into multiple syringes.

Dose Adjustments

- For severe or clinically significant transaminase elevations with dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly

Drug Availability

- 189 mg/mL in a single-dose vial

PRECAUTIONS:

Boxed Warning

- none

Contraindications

- Severe hypersensitivity to givosiran

Precautions/Warnings

- Anaphylactic reaction: Ensure medical support is available to manage anaphylactic reactions
- Hepatic toxicity: Measure liver function at baseline and periodically during treatment. Interrupt or discontinue treatment

- Renal toxicity: Monitor renal function during treatment as clinically indicated
- Injection site reactions: May occur, including recall reactions; monitor and manage clinically as needed.
- Blood Homocysteine Increased: Measure blood homocysteine at baseline and monitor for changes during treatment with givosiran. In patients with elevated blood homocysteine, consider supplementation with vitamin B6 (as monotherapy or multivitamin).
- Pancreatitis: Consider acute pancreatitis as a potential diagnosis in patients with acute upper abdominal pain, clinically significant elevation of pancreatic enzymes and/or imaging findings of acute pancreatitis, to ensure appropriate management.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0223	Injection, givosiran, 0.5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E80.21	Acute intermittent (hepatic) porphyria

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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5. Givlaari (givosiran)[package insert]. Alnylam Pharmaceuticals, Inc. Cambridge MA. April 2024
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [2024 Aug 30]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
7. Sardh E, Harper P, Balwani M. et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med. 2019; 380: 549-58.
8. The Porphyrias Consortium. https://www.rarediseasesnetwork.org/cms/porphyrias/Healthcare-Professionals/Disorder-Definitions
9. Wang, B, Rudnick S, Cengia B, Bonkovsky HL. Acute Hepatic Porphyrias: Review and recent progress. Hepatology communications. 2019; 3 (2): 193-206.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/24.

GUIDELINE UPDATE INFORMATION:

03/15/20	New Medical Coverage Guideline.
04/01/20	HCPCS Update: Added code C9056.
07/01/20	Revision: Added HCPCS code J0223 and deleted codes C9056 and J3490.
08/15/20	Review and revision to guideline including updating the position statement.
08/15/21	Review and revision to guideline including updating references.
04/15/22	Review and revision to guideline; including updating references.
04/15/23	Review and revision to guideline; including updating references.
10/15/24	Review and revision to guideline; including updating references.