Givlaari (givosiran)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Givlaari is indicated for the treatment of adults with acute hepatic porphyria (AHP). 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. This leads to reduced circulating levels of neurotoxic intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. Initial Therapy Requests
    1. Elevated porphobilinogen (PBG) in the urine confirmed by a PBG quantitative, random urine test, or an elevated porphyrin level (plasma or fecal).
B. Continuation of Therapy Requests
    1. Documentation supporting the positive clinical response to Givlaari therapy from pre-treatment baseline (e.g., chart notes, laboratory values)

Criteria for Initial Approval

A. Givlaari may be considered **medically necessary** for the treatment of acute hepatic porphyria when the following criteria are met:
   1. The member is 18 years of age or older
   2. The member has a diagnosis of acute hepatic porphyria (AHP) [i.e., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, or ALA dehydratase deficient porphyria]
   3. The medication is prescribed by, or in consultation with, a specialist in acute hepatic porphyria treatment (e.g., hepatologist, hematologist, or neurologist)
   4. The member has active disease defined as 2 documented porphyria attacks within the past 6 months requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home
   5. The member has an elevated porphobilinogen (PBG), or an elevated porphyrin level (plasma or fecal)
   6. The member will not receive concomitant prophylactic hemin treatment while on Givlaari (this does not include hemin used for treatment of acute porphyria attacks)
   7. The member has not had nor anticipates a liver transplantation
   8. The requested medication will be administered by a healthcare professional with medical support available to manage potential anaphylactic reactions

Approval will be for up to **6 months**

Continuation of Therapy

A. Givlaari may be considered **medically necessary** for the continuation of treatment of acute hepatic porphyria when the following criteria is met:
   1. The member is 18 years of age or older
   2. The member has a diagnosis of acute hepatic porphyria (AHP) [i.e., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, or ALA dehydratase deficient porphyria]
   3. The medication is prescribed by, or in consultation with, a specialist in acute hepatic porphyria treatment (e.g., hepatologist, hematologist, or neurologist)
   4. The member will not receive concomitant prophylactic hemin treatment while on Givlaari (this does not include hemin used for treatment of acute porphyria attacks)
   5. The member has not had nor anticipates a liver transplantation
   6. Member has experienced a positive clinical response while on Givlaari therapy as demonstrated by ALL of the following:
      - A reduction from baseline in the number of porphyria attacks that required hospitalization, urgent healthcare visits, or intravenous hemin administration
      - A reduction in hemin administration requirements (if previously required)
      - Improvement in the signs and symptoms of the disease (i.e., abdominal pain, neurological, gastrointestinal)
   7. Member does not experience serious side effects (i.e., anaphylactic reactions, renal or hepatic toxicity)

Approval will be for up to **12 months**

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

The recommended dose of Givlaari is 2.5mg/kg administered subcutaneously by a healthcare professional once monthly.

CLINICAL RATIONALE

Acute hepatic porphyria (AHP) is a collection of four rare, genetic diseases characterized by a deficiency in one of the enzymes involved in heme biosynthesis, resulting in an accumulation of toxic heme intermediates which can cause acute attacks. Patients experiencing an acute attack may present with neuropathic abdominal pain and gastrointestinal symptoms. Patients may also experience seizures, heart palpitations, and acute psychiatric symptoms. There are no standard published guidelines for the treatment of AHP. The current standard of care for patients experiencing an acute attack is intravenous hemin therapy, although oral or intravenous carbohydrate loading can be given in patients experiencing a mild attack. Patients should also receive symptomatic care.

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. This leads to reduced circulating levels of neurotoxic intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

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. 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. On average, AHP patients on Givlaari experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo. Givlaari also resulted in a reduction in hemin use, urinary ALA, and urinary PBG.

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. 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%).

Based upon the clinical trial, Givlaari appears to decrease the number of acute attacks and days on hemin therapy, which is the standard of care. Regarding safety, Givlaari is associated with anaphylaxis, hepatic and renal toxicity, and injection site reactions. The most common adverse events were nausea, injection site reactions, rash, increased serum creatinine, transaminase elevations, and fatigue.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- C9056 injection, givosiran, 0.5 mg (deleted 6-30-2020)
- J0223 injection, givosiran, 0.5 mg (added 7-1-2020)

REFERENCES

- Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; December 2019.
- ENVISION: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients with Acute Hepatic Porphyrias (AHP). Available at: https://clinicaltrials.gov/ct2/show/NCT03338816. Accessed March 31, 2020.
- Stölzel U, Doss MO, Schuppan D. Clinical Guide and Update on Porphyrias. Gastroenterology. 2019 Aug; 157(2):365-381.
- Kothadia JP, LaFreniere K, and Shah JM. Acute hepatic porphyria. 2019 September. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537178/. Accessed March 31,2020.

*Some content reprinted from CVSHealth

POLICY HISTORY

Policy #: 05.04.02
Policy Creation: April 2020
Reviewed: January 2021
Revised:
Current Effective Date: June 18, 2020