Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 02/08/2024

Givlaari® (givosiran)

HCPCS: J0223

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of Acute Hepatic Porphyria (AHP) which includes: ALA-Dehydratase Deficiency Porphyria (ADP), Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), or Variegate Porphyria (VP)
   c. Documentation of elevated urinary aminolevulinic acid (ALA) OR porphobilinogen (PBG) levels above the lab test upper limit of normal obtained during an acute attack AND/OR genetic testing positive for a mutation consistent with ADP, AIP, HCP, or VP
   d. Have active disease with at least 2 documented porphyria attacks in the last 6 months OR chronic baseline disease activity with symptoms such as:
      i. Pain in the abdomen, back, and/or chest
      ii. Cardiovascular conditions including hypertension and tachycardia
      iii. Gastrointestinal involvement including nausea, vomiting, and constipation
      iv. Neurological involvement including neuropathic pain, sensory loss, muscle weakness, paralysis, confusion, anxiety, depression, memory loss, fatigue, hallucinations, seizures
      v. Other system involvement including respiratory failure, skin lesions, hyponatremia
   e. Have taken the appropriate lifestyle modifications to prevent acute attacks including, but not limited to: dietary modifications, quitting smoking, stopping alcohol use, and removing medications known to cause acute attacks when possible
   f. Must not have had a previous liver transplant or have a scheduled liver transplant
   g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Acute Hepatic Porphyria (AHP) is a rare, autosomal dominant disorder with 4 different variations (Acute Intermittent Porphyria, Hereditary Coproporphyria, Variegate Porphyria, and ALA Dehydratase-Deficient Porphyria) that results from a partial deficiency in 4 enzymes that are part of the heme biosynthetic pathway leading to an accumulation of toxic heme intermediaries, aminolevulinic acid (ALA) and porphobilinogen (PBG), which are thought to cause the clinical manifestations of AHP.

- An estimated 5,000 patients in the US and Europe suffer from AHP attacks annually, and 500 to 1,000 experience recurrent attacks. The incidence and prevalence of AHP in Sweden is 4 times as high compared to the rest of Europe.

- Signs and symptoms of AHP are generally nonspecific and typically occur as intermittent acute attacks that are sometimes life-threatening. The most common symptoms include abdominal pain, vomiting, constipation, muscle weakness, psychiatric symptoms, hypertension, painful urination, and urinary retention or incontinence. Acute attacks are usually associated with exacerbating factors, such as medications, smoking, sex hormones, fasting and stress.

- Most patients have a complete resolution in their symptoms between attacks; however, some patients develop chronic symptoms including pain requiring opioid analgesics, depression/anxiety, and persistent hypertension.

- The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network (2017) guidelines provide the following recommendations for long-term management of AHP:

    - Management should focus on the identification and avoidance of factors that precipitate or worsen acute AHP attacks. Patients should be counseled to avoid certain environmental triggers, including certain medications, crash dieting or fasting-type dieting, smoking (tobacco and marijuana), and alcohol.

    - Prophylactic therapy with hemin or intravenous glucose can decrease ALAS-1 activity after 2-3 infusions, with hemin having a more potent effect. Hemin is often used for more severe attacks while glucose loading is used for only mild attacks with improvement in symptoms generally seen within 3-4 days. Patients who experience four or more attacks per year may require hemin prophylaxis up to twice weekly; however, some patients do report improvement with monthly infusions.

    - Severe iron overload can occur with recurrent heme administration leading to the necessity of therapeutic phlebotomy when ferritin levels are >1000 ng/mL.

    - Supportive therapy to address symptoms of AHP may be needed, including pain medications (such as opioids), electrolyte replacement, anticonvulsants, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and calcium channel blockers.

    - Liver transplantation is a last-line option for AHP which has been shown to be curative; however, due to significant morbidity and mortality associated with liver transplantation, this surgical procedure is reserved for those with severe, disabling, intractable attacks that are refractory to hemin therapy.

- Clinical trials assessing Givlaari as treatment in AHP were ongoing at the time of publication of the Porphyria Consortium's guidelines (2017); therefore, current guidelines do not include recommendations for Givlaari in the setting of AHP.

- The American Gastroenterological Association (AGA) Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review (2023) provides additional recommendations regarding the diagnosis and management of AHP including the following Best Practice Statements:

  - Initial diagnosis of AHP should be made by biochemical testing measuring ALA, PBG, porphyrins, and creatinine in a random urine sample.

  - Genetic testing should be used to confirm the diagnosis of AHP in patients with positive biochemical testing.

  - Prophylactic heme therapy or givosiran, administered in an outpatient setting, should be considered in patients with recurrent attacks (4 or more per year).

- Givlaari (givosiran) is the first and only FDA-approved therapy for the treatment of adults with AHP. Givlaari is a double-stranded small interfering RNA (siRNA) which acts in the liver to reduce circulating levels of neurotoxic intermediaries, ALA and PBG.

- Givlaari was evaluated in a Phase III, double-blind, placebo-controlled trial (ENVISION, NCT03338816), which enrolled 94 patients ages 12 years of age and older with symptomatic AHP and at least 2 documented porphyria attacks within the last 6 months. Of the 94 patients enrolled in the trial, 89 had Acute Intermittent Porphyria, 1 had Hereditary Coproporphyria, 2 had Variegate Porphyria, and 2 had Acute Hepatic Porphyria without an identified mutation.

  - Methods: Patients were randomized to receive once monthly injections of either subcutaneous Givlaari at a dose of 2.5 mg/kg (N=48) or placebo (N=46) for a total of 6 months.

  - Endpoints: The primary endpoint was reduction relative to placebo in the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria (the most common subtype of AHP), defined as attacks requiring hospitalization, an urgent healthcare visit, or hemin administration. Key secondary endpoints included evaluation of ALA and PGP levels in addition to hemin use in patients with Acute Intermittent Porphyria.

  - Results:

    - Primary endpoint: In patients with Acute Intermittent Porphyria, the average annualized rate of composite porphyria attacks over 6 months was 3.2 (95% CI: 2.3 – 4.6) in the Givlaari group compared to 12.5 (95% CI: 9.4 – 16.8) in the placebo group, representing a 74% lower rate of averaged annualized attacks for the Givlaari group ($p<0.001$). Results were similar for patients with other subtypes of AHP.

    - Secondary endpoints: Among patients with Acute Intermittent Porphyria, treatment with Givlaari led to significantly lower levels of urinary ALA and PGP and fewer days of hemin use (6.8 days v. 29.7 days) compared to the placebo.

References:

1. Givlaari® [package insert]. Alnylam Pharmaceuticals, Inc.; Cambridge, MA, November 2019.
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3. Balwani M, Sardh E, Ventura P, et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. N Engl J Med. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147
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<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.6</td><td>Effective Date: 02/08/2024</td><td>Updated to remove the specialist prescriber requirement and change the renewal criteria to standard language</td></tr>
<tr><td>1.5</td><td>Effective Date: 02/03/2023</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.4</td><td>Effective Date: 02/10/2022</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 02/04/2021</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.2</td><td>Effective Date: 06/01/2020</td><td>UM medical management system update for MAPPO and BCNA
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*