PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Givlaari Prior Authorization Policy
- Givlaari™ (givosiran injection solution, for subcutaneous use – Alnylam Pharmaceuticals)

REVIEW DATE: 12/16/2020

OVERVIEW

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

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] Heme is necessary for the transport of oxygen to cells in the body. If synthesis of heme is hindered, an accumulation of porphyrins or porphyrin precursors (intermediate chemicals) accumulates in the cells, resulting in oxygen depletion. 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. Hospitalization is often required for acute attacks. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrent occurrences may develop chronic pain. Due to the high prevalence of chronic kidney disease, serum creatinine and estimated glomerular filtration rate should be monitored annually for all symptomatic patients.

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 to 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Givlaari. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Givlaari as well as the monitoring required for adverse events and long-term efficacy, approval requires Givlaari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Givlaari is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Acute Hepatic Porphyria.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Diagnosis of acute hepatic porphyria was confirmed by both of the following (i and ii):
     - **i.** Patient demonstrated clinical features associated with acute hepatic porphyria; AND
       Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
       - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
   - **C)** Prior to starting treatment with Givlaari, the patient has a history of one porphyria attack in the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration at home; AND
   - **D)** Givlaari is prescribed by, or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Givlaari is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Givlaari™ injection solution [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals; November 2019.
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 November 30, 2020.
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.