

givosiran (Givlaari™)

Medicare Advantage Medical Policy #MNG-059

Original Effective Date: 02/01/2025

Current Effective Date: 02/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider givosiran (Givlaari™)‡ for the treatment of acute hepatic porphyria to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for givosiran (Givlaari) will be considered when the following criteria are met:

I. Initial therapy:

- A. Patient has a diagnosis of Acute Hepatic Porphyria [AHP] (e.g., Acute Intermittent Porphyria [AIP], Hereditary Coproporphyrinemia [HCP], Variegate Porphyria [VP], aminolevulinic acid [ALA] dehydratase deficient porphyria [ADP]) confirmed by BOTH of the following (i AND ii):
 - i. Presence of symptoms consistent with AHP diagnosis; AND
 - ii. ONE of the following (a OR b):
 - a. Elevated urinary porphobilinogen [PBG] or ALA within the past year (e.g., PBG >10 mg/g creatinine or PBG >10 mg/L); OR
 - b. Documentation of genetic testing confirming pathogenic mutation in a gene encoding a heme synthesis enzyme (e.g., *ALAS*, *ALAD*, *PBGD*, *UROS*, *UROD*, *CPOX*, *PPOX*, *FECH*); AND
- B. Patient is ≥18 years of age; AND
- C. Liver transplantation has not occurred and is not anticipated; AND
- D. Patient has experienced at least two porphyria attacks requiring hospitalization, urgent healthcare visit, or heme administration in the past 6 months OR has a history of one severe attack with central, autonomic, or peripheral nervous system involvement (e.g., hallucinations, seizures, respiratory failure, paralysis, etc.); AND
- E. Requested dose does not exceed 2.5 mg/kg once monthly.

II. Continuation therapy:

- A. Patient received an initial authorization for Givlaari from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
- B. Patient has demonstrated a beneficial response to Givlaari (e.g., reduction in attacks); AND
- C. Liver transplantation is not anticipated and has not occurred since the previous authorization; AND
- D. Requested dose does not exceed 2.5 mg/kg once monthly.

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of givosiran (Givlaari) when the patient is anticipating or has received a liver transplant or for patients who have not experienced at least two porphyria attacks in the previous 6 month or one severe attack with autonomic, central, or peripheral nervous system involvement to be **not medically necessary.****

Based on review of available data, the Health Plan considers the continued use of givosiran (Givlaari) when the patient has not responded to therapy or has received or is anticipating receiving a liver transplant to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of givosiran (Givlaari) when patient selection criteria are not met (except for those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Givlaari is a small interfering RNA (siRNA) therapeutic that is directed against the hepatic *ALAS1* gene and is indicated for treatment of adults with acute hepatic porphyria (AHP). Patients with this condition have a genetic mutation that ultimately leads to accumulation of the neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG). By reducing the elevated levels of *ALAS1* mRNA, Givlaari reduces the production and therefore the circulating levels of ALA and PBG to reduce the disease manifestations of AHP. Givlaari is dosed as a 2.5 mg/kg once monthly subcutaneous injection that must be administered by a healthcare provider.

AHPs are a group of rare metabolic disorders that include acute intermittent porphyria (AIP), variegate porphyria (VP), ALA dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP). These conditions occur in around 5 per 100,000 persons. Each of these conditions is caused by a genetic abnormality that results in an enzyme deficiency in the liver leading to accumulation of porphyrins such as ALA and PBG. 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 and these attacks may be life-threatening. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrent occurrences may develop chronic pain.

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Prior to the availability of Givlaari, hemin (Panhematin®)‡ was the mainstay of treatment for AHP. Panhematin is an enzyme inhibitor derived from processed red blood cells and is only indicated for the amelioration of recurrent attacks of AIP temporally related to the menstrual cycle in susceptible women. However, it is widely used off-label in the AHP population to treat acute attacks and as prophylaxis in patients with severe disease. Guidelines from the Porphyrrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network (2017) recommend hemin for preventative management in AHP and treatment during acute attacks. Patients with ≥ 4 attacks per year are candidates for either prophylactic or "on demand" infusions and 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 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, administering a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or giving prophylactic hemin therapy infusions. Orthotopic liver transplantation is considered a last resort treatment in patients who are refractory to hemin therapy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Givlaari was approved in November 2019 for the treatment of adults with acute hepatic porphyria.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Givlaari in patients with acute hepatic porphyria was evaluated in the ENVISION trial, a randomized, double-blind, placebo-controlled, multinational study of 94 patients with acute hepatic porphyria. Of the enrolled patients, 89 had AIP, 2 had VP, 1 had HCP, and 2 had no identified mutation. Patients were randomized 1:1 to either receive monthly subcutaneous injections of Givlaari 2.5 mg/kg or placebo for 6 months. 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.

Efficacy was measured by the rate of porphyria attacks that required hospitalizations, urgent healthcare visits, or intravenous hemin administration at home. On average, AHP patients on Givlaari experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo. The mean rate of attacks in the Givlaari group (n=48) was 1.9 (95% CI 1.3, 2.8) and it was 6.5 (95% CI:

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4.5, 9.3) in the placebo group (n=46). Givlaari also resulted in a reduction in hemin use, urinary ALA, and urinary PBG.

References

1. Givlaari [package insert]. Alnylam Pharmaceuticals, Inc. Cambridge, MA. Updated December 2019.
2. Acute intermittent porphyria: Pathogenesis, clinical features, and diagnosis. UpToDate. Updated September 2018.
3. Givlaari Drug Evaluation. Express Scripts. Updated December 2019.
4. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: Recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

Policy History

Original Effective Date: 02/01/2025

Current Effective Date: 02/01/2025

11/19/2024 UM Committee review. New policy.

Next Scheduled Review Date: 11/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Code Type	Code
CPT	No codes
HCPCS	J0223
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.