UnitedHealthcare® Community Plan

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Medical Benefit Drug Policy

GIVLAARI (GIVOSIRAN)

Policy Number: CS2020D0087A **Effective Date: TBD**

Instructions for Use

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COVERAGE RATIONALE

Givlaari is proven and/or medically necessary for the treatment of acute hepatic porphyrias:[1-4]

Initial Therapy

- Diagnosis of an acute hepatic porphyria (i.e., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, ALA dehydratase deficient porphyria); and
- One of the following:
  - Patient has active disease as defined in the clinical trial by having at least 2 documented porphyria attacks within the past 6 months; or
  - Patient is currently receiving treatment with prophylactic hemin to prevent porphyria attacks

  and
- Provider attestation that the patient's baseline (before givosiran is initiated) hemin administration requirements (prophylactic or treatment) and rate and/or number of porphyria attacks has been documented; and
- Patient has not had a liver transplant; and
- Patient will not receive concomitant prophylactic hemin treatment while on Givlaari; and
- Prescribed by, or in consultation with, a hematologist, or a specialist with expertise in the diagnosis and management of AHPs; and
- Givlaari dosing is in accordance with the United States Food and Drug Administration approved labeling: up to a maximum of 2.5 mg/kg (body weight) subcutaneously once monthly; and
- Initial authorization will be for no more than 6 months

Continuation Therapy

- Patient has previously received Givlaari for the treatment of AHP; and
- Documentation that the patient has experienced a positive clinical response while on Givlaari by demonstrating all of the following from pre-treatment baseline:
  - Reduction in hemin administration requirements (if previously required, including prophylactic and/or treatment doses);
  - Reduction in the rate and/or number of porphyria attacks;
  - Improvement of signs and symptoms of AHPs (e.g., pain, neurological, gastrointestinal, renal, quality of life, etc.)

  and
- Patient has not had a liver transplant; and

- **Patient will not receive concomitant prophylactic hemin treatment while on Givlaari; and**
- **Prescribed by, or in consultation with, a hematologist, or a specialist with expertise in the diagnosis and management of AHPs; and**
- **Givlaari dosing is in accordance with the United States Food and Drug Administration approved labeling: up to a maximum of 2.5 mg/kg (body weight) subcutaneously once monthly; and**
- **Reauthorization will be for no more than 12 months**

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

BACKGROUND

Acute hepatic porphyria refers to a family of ultra-rare genetic diseases that lead to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver. Severe, unexplained abdominal pain is the most common symptom, which can be accompanied by limb, back, or chest pain, nausea, vomiting, confusion, anxiety, seizures, weak limbs, constipation, diarrhea, or dark or reddish urine. Long-term complications and comorbidities of AHP can include hypertension, chronic kidney disease or liver disease including hepatocellular carcinoma. Currently, the population of AHP patients with diagnosed, active disease in the U.S. and Europe is estimated to be approximately 3,000.

Givosiran 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 aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

CLINICAL EVIDENCE

The efficacy of Givlaari was established in the Phase 3 ENVISION trial, a randomized, double-blind, placebo-controlled multicenter study in 94 patients with AHP (89 patients with acute intermittent porphyria (AIP), 2 patients with variegate porphyria [VP], 1 patient with hereditary coproporphyria [HCP], and 2 patients with no identified mutation). 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. Patients were randomized to receive Givlaari or placebo during. 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. The mean rate of porphyria attacks was 1.9 and 6.5 for Givlaari and placebo, respectively. This represented a 70% (95% CI: 60, 80) reduction in porphyria attacks for patients receiving Givlaari vs. placebo. The mean number of days of hemin use was 4.7 (95% CI: 2.8, 7.9) with Givlaari vs. 12.8 (95% CI: 7.6, 21.4) with placebo.[1]

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Givlaari (givosiran) is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP). The recommended dose of Givlaari is 2.5 mg/kg administered via subcutaneous injection once monthly. Dosing is based on actual body weight.[1]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for GIVLAARI™ (givosiran). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed November 21, 2019)

REFERENCES

1. Givlaari [package insert]. Summit, NJ: Celgene Corporation, November 2019.
2. ENVISION: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP). Clinicaltrials.gov website https://clinicaltrials.gov/ct2/show/NCT03338816?term=givosiran&cond=porphyria&draw=1&rank=5 Accessed November 21, 2019.
3. 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 Feb 7;380(6):549-558.
4. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. Hepatology. 2017 Oct;66(4):1314-1322.
5. Stölzel U, Doss MO, Schuppan D. Clinical Guide and Update on Porphyrias. Gastroenterology. 2019 Aug;157(2):365-381.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	• New Medical Benefit Drug Policy

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.