

Corporate Medical Policy

Givosiran (Givlaari™)

File Name:	givosiran_givlaari
Origination:	2/2020
Last CAP Review:	5/2020
Next CAP Review:	5/2021
Last Review:	9/2020

Description of Procedure or Service

Givosiran (Givlaari) is an aminolevulinic acid synthase 1-directed small interfering RNA that is indicated for the treatment of adult patients with acute hepatic porphyria (AHP).

Porphyrias are inherited metabolic disorders that are caused by altered enzyme activity within the heme biosynthetic pathway, which is responsible for production of oxygen-carrying components of red blood cells. Acute hepatic porphyria (AHP), a form of porphyria, results in the accumulation of toxic porphyrin molecules which are formed during the production of heme and is comprised of four prototypes: acute intermittent porphyria (most common), hereditary coproporphyria, variegate porphyria, and aminolevulinic acid (ALA) dehydratase deficient porphyria. The buildup of toxins (porphyrins) in AHP patients causes acute life-threatening attacks of non-specific neurologic symptoms, most commonly severe neuropathic abdominal pain, and can lead to long-term complications such as hypertension, chronic renal failure, liver disease, and hepatocellular carcinoma. Prior to the approval of givosiran, the only approved treatment for recurrent porphyria attacks in AHP was the intravenous administration of hemin (Panhematin), together with carbohydrate loading and other supportive care. However, hemin has not been approved for prophylactic treatment. Liver transplantation has also been considered as a final treatment option in patients with severe intractable manifestations of AHP.

Givosiran (Givlaari) is a double-stranded small interfering RNA that was approved by the U.S. Food and Drug Administration (FDA) in November 2019 for the treatment of acute hepatic porphyria. It works by causing degradation of aminolevulinic acid synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, which reduces the elevated levels of *ALAS1* mRNA in the liver. This leads to decreased circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) that are associated with attacks and other AHP manifestations.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for givosiran (Givlaari) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Givosiran (Givlaari) is covered

Initial Therapy

Givosiran (Givlaari) is considered medically necessary in adult patients (≥ 18 years of age) with acute hepatic porphyria (AHP) when the following criteria are met:

1. The patient has a confirmed diagnosis of acute hepatic porphyria (including acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria); AND
2. The patient has documentation of elevated urinary or plasma porphobilinogen (PBG) or ALA values; AND
3. The patient has had one of the following:
 - a. History of at least two documented porphyria attacks within the 6 months prior to initiation (requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home), OR
 - b. History of one severe attack within the past year with central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS) involvement (e.g., hallucinations, seizures, respiratory failure, paralysis); AND
4. The patient has not had nor is anticipating a liver transplantation; AND
5. Givosiran is prescribed by or in consultation with a specialist in porphyria treatment (e.g. hepatologist, hematologist, neurologist)

Initial authorization: 6 months

Continuation Therapy

Continuation of treatment with givosiran (Givlaari) beyond 6 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of acute hepatic porphyria when the following criteria are met:

1. The patient is currently receiving givosiran and continues to meet initial criteria; AND
2. The patient has a positive clinical response as demonstrated by a reduction in porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration

When Givosiran (Givlaari) is not covered

Givosiran (Givlaari) is considered **investigational** and therefore not covered when the above criteria are not met.

Policy Guidelines

The recommended dose of Givlaari is 2.5 mg/kg administered as a subcutaneous injection once monthly. Givlaari must be administered by a healthcare professional only. Medical support

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should be readily available to appropriately manage anaphylactic reactions that may occur when administering Givlaari.

According to the manufacturer's safety information for Givlaari, the most common adverse reactions ($\geq 20\%$ incidence) include nausea and injection site reactions. Anaphylaxis reactions have occurred with Givlaari treatment. Medical support should be readily available to appropriately manage anaphylactic reactions during Givlaari administration. Other warnings and precautions associated with Givlaari treatment are hepatic and renal toxicity. Liver function should be measured at baseline and periodically during Givlaari treatment, and treatment should be interrupted or discontinued if severe or clinically significant transaminase elevations occur. Renal function should also be monitored during Givlaari treatment when clinically indicated.

Clinical Trial Evidence

The efficacy of givosiran in patients with acute hepatic porphyria (AHP) was assessed in a randomized, double-blind, placebo-controlled, multinational clinical trial (ENVISION trial; NCT03338816). The study enrolled 94 patients with AHP (89 patients with acute intermittent porphyria, 2 patients with variegate porphyria, 1 patient with hereditary coproporphyrin, and 2 patients with no identified mutation) with a minimum of two porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in the 6 months prior to trial entry. Patients were randomized 1:1 to receive once monthly subcutaneous injections of either givosiran 2.5 mg/kg or placebo over a 6-month double-blind period. Use of hemin was allowed during the study for the treatment of acute porphyria attacks. The primary efficacy endpoint was the rate of porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration at home, which was significantly lower with givosiran treatment (mean rate, 1.9; 95% CI, 1.3 to 2.8) compared to placebo (mean rate, 6.5; 95% CI, 4.5 to 9.3). According to the prescribing information for givosiran, study results suggest that AHP patients receiving givosiran experienced 70% fewer porphyria attacks than patients receiving placebo (95% CI, 60% to 80%).

The following information is derived from FDA prescribing information, as peer reviewed published trial results have not been identified.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J0223

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Alnylam. Givlaari (givosiran) injection, for subcutaneous use. Highlights of prescribing information. November 2019. Available at: <https://www.alnylam.com/wp-content/uploads/pdfs/GIVLAARI-Prescribing-Information.pdf>. Last accessed February 2020.

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U.S. Food and Drug Administration. FDA approves first treatment for inherited rare disease. November 2019. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-inherited-rare-disease>. Last accessed February 2020.

Stölzel U, Doss MO, Schuppan D, et al. Clinical guide and update on porphyrias. *Gastroenterology* 2019;157(2):365-81. Available at: [https://www.gastrojournal.org/article/S0016-5085\(19\)40883-4/pdf](https://www.gastrojournal.org/article/S0016-5085(19)40883-4/pdf). Last accessed February 2020.

Kauppinen R. Porphyrias. *Lancet* 2005;365:241-52.

Medical Director review 2/2020

Specialty Matched Consultant Advisory Panel review 5/2020

Medical Director review 9/2020

Policy Implementation/Update Information

- 2/11/20 New policy developed. Givosiran (Givlaari) is considered medically necessary in adult patients (≥ 18 years of age) with acute hepatic porphyria (AHP) when specified medical criteria and guidelines are met. Added HCPCS codes C9399 and J3490 to Billing/Coding section. References added. Medical Director review 2/2020. (krc)
- 3/31/20 Added HCPCS code C9056 to Billing/Coding section effective 4/1/2020. (krc)
- 6/23/20 Specialty Matched Consultant Advisory Panel review 5/20/2020. No change to policy intent. (krc)
- 6/30/20 Added HCPCS code J0223 to Billing/Coding section effective 7/1/2020 and deleted code C9056, C9399, J3490 termed 6/30/2020. (krc)
- 9/22/20 Added the following criteria to “When Covered” section “History of one severe attack within the past year with central nervous system (CNS), autonomic nervous system (ANS), or peripheral nervous system (PNS) involvement (e.g., hallucinations, seizures, respiratory failure, paralysis).” Medical Director review 9/2020. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.