Policy Number	**RX501.125**
Policy Effective Date	**12/15/2024**

Givosiran

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Givosiran (Givlaari®) **may be considered medically necessary** for the treatment of individuals with acute hepatic porphyria (AHP) who meet the following criteria:

- Individuals 18 years of age and older; **AND**
- Patient has a confirmed diagnosis of acute hepatic porphyria (AHP) (i.e., acute intermittent porphyria [AIP], variegate porphyria [VP], hereditary coproporphyria [HCP], delta-aminolevulinic acid dehydratase deficient porphyria [ADP]); **AND**
- Patient has active disease with at least two documented porphyria attacks within the 6 months prior to initiation (requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home).

Givosiran (Givlaari®) **is considered experimental, investigational, and/or unproven** for all other indications.

NOTE: Givosiran (Givlaari®) is a subcutaneous injection administered by a healthcare provider.

Policy Guidelines

None.

Description

Givosiran is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP).

Acute Hepatic Porphyrias
Acute hepatic porphyrias includes a family of rare, genetic diseases in which there is a defect, or deficiency, in one of the enzymes within the heme biosynthetic pathway in the liver that can result in accumulation of porphyrins, a heme precursor that can be toxic to the tissues at high levels, and neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG). Hepatic porphyrias is comprised of four subtypes which include acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), which are autosomal dominant disorders, and aminolevulinic acid dehydratase deficiency porphyria (ALAD), which is autosomal recessive and very rare. (2, 7)

<u>Acute Intermittent Porphyria (AIP)</u>

AIP is also called Swedish porphyria, pyrroloporphyria, intermittent acute porphyria. It is the most common of the acute porphyrias worldwide, with a roughly estimated prevalence of approximately 50 per million, probably including asymptomatic cases. AIP occurs in all races but may be most common in northern Europeans; and is more likely to manifest in women than men. It typically presents in the third or fourth decade of life; and acute attacks are rare before puberty. (3)

Hereditary Coproporphyria (HCP)

HCP is an inherited condition characterized by acute neurovisceral as well as chronic blistering cutaneous manifestations. The neurovisceral manifestations are indistinguishable from those of other AHP (AIP, VP, and delta-aminolevulinic acid [ALA] dehydratase porphyria [ADP]), and the chronic cutaneous manifestations are similar to the other chronic blistering cutaneous porphyrias (porphyria cutanea tarda [PCT], VP, and hepatoerythropoietic porphyria [HEP]). HCP has also been called "mixed porphyria," an obsolete term that was also applied to VP. The prevalence of HCP has been estimated at approximately two to five per million population. It is found throughout the world and is more common in females than males, typically manifesting after puberty. It is less common than AIP and VP, but more common than delta-aminolevulinic acid (ALA) dehydratase porphyria (ADP). (4)

Variegate Porphyria

VP is an inherited porphyria characterized by cutaneous blistering and/or acute neurovisceral attacks. VP has also been called porphyria variegata, South African genetic porphyria, mixed porphyria (an obsolete term also applied to HCP), protocoproporphyria, and porphyria cutanea tarda hereditaria (which likely included some cases of familial PCT). Occurring worldwide, the prevalence of VP is not accurately known as many individuals with the protoporphyrin oxidase (PPOX) mutations remain asymptomatic. The prevalence of symptomatic VP has been estimated at 0.3 per 100,000 in Europe (approximately 1 in 300,000). Some countries such as Finland may have a higher prevalence of VP (1.3 in 100,000; equivalent to approximately 1 in 77,000). It is high in South Africans of Dutch descent (1 in 300) because a Dutch ancestor carried the PPOX founder mutation R59W and the population expanded greatly while remaining quite isolated for many years. As many as 30,000 individuals in South Africa carry this PPOX mutation. Typically presenting after puberty, during adolescence or early adulthood, women are more commonly symptomatic for both skin and neurovisceral symptoms than men. (5)

Delta-Aminolevulinic Acid (ALA) Dehydratase (ALAD) Porphyria (ADP)

Delta-aminolevulinic acid (ALA) dehydratase (ALAD) porphyria (ADP), also called Doss porphyria and plumboporphyria, is the rarest of the inherited porphyrias, with only eight documented cases worldwide. All male, two cases were identified at birth; one at age 7; four at the age of 12 to 15 years (three in Germany and one in the United States); and a 63-year-old Belgian man. Greater awareness of porphyrias appears to account for occurrence of the seven cases documented in Europe. (6)

Symptoms

AHPs are characterized by episodic neurological attacks (seizures, psychosis, severe abdominal and back pain, and an acute polyneuropathy), which can occur suddenly and can produce permanent neurological damage and death; and, to a lesser extent, present with cutaneous manifestations, usually a photosensitive blistering rash or hypertrichosis. The most common presenting symptom is neuropathic abdominal pain. Management of these individuals can be challenging because the disease manifestations are diverse and potentially life-threatening due to neurologic complications (e.g., seizures or paralysis). (2, 7)

Evaluation

Evaluating a person for AHP involves a detailed history, a thorough physical examination, and follow-up when AHP is suspected. "Urine porphobilinogen (PBG) is the most important first-line screening test, which is both highly sensitive and highly specific. Through feedback, the reduced production of heme brings about elevated production of heme precursors, with PBG among the first substances in the porphyrin synthesis pathway. In fact, in almost all cases of acute hepatic porphyrias, urinary PBG is significantly elevated. Of note, repeat testing during an acute attack may be needed to diagnose a porphyria, as levels may be normal or almost normal between attacks." (7) Plasma and feces can be tested for quantitative determination of ALA, PBG, and porphyrin levels. Decreased erythrocyte porphobilinogen deaminase (PBGD) activity is seen in the approximately 90% of patients. It can also be seen in asymptomatic patients. Mild elevation of transaminases is common, but other liver function tests generally remain normal. Kothadia et al. (7) note that AHPs are very rare diseases and that general hospital labs usually do not have the technology, the staff time, or the expertise to conduct testing for them. Commonly, such testing involves sending the samples of blood, urine, and stool to a reference laboratory.

Therapy

Therapy requires confirmation that the individual indeed has acute porphyria, based on the finding of elevated urinary PBG, either at present or previously, but it does not require a diagnosis of the exact type of acute porphyria. (7) The goal of treatment for an acute attack of hepatic porphyria has been to abate the attack as quickly as possible and to provide appropriate supportive care and symptomatic care until the acute attack resolves. Treatment of acute attacks include intravenous administration of hemin, especially for those individuals requiring hospitalization, opioid analgesia, or condition is accompanied by nausea/vomiting, motor neuropathy, paresis, seizures, agitation, delirium, psychosis, ileus or hyponatremia. Carbohydrate loading is also recommended as a temporary measure if hemin is not immediately available. Glucose and other carbohydrates reduce excretion of porphyrin precursors by downregulating hepatic ALAS enzyme, delta-aminolevulinic acid synthase (ALAS1), an effect mediated by decreases in the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha). However, the effects of glucose are weak compared with those of hemin. (3, 7, 8) In contrast to acute attacks, subacute or chronic symptoms are unlikely to respond to acute administration of hemin. Hemin represses hepatic delta-aminolevulinic acid synthase (ALAS1) for only a few days before it is rapidly metabolized to biliverdin and bilirubin by hepatic heme oxygenase and biliverdin reductase. A trial of hemin may be warranted in persons with subacute symptoms, but chronic pain and other symptoms are treated symptomatically, often with consultation with a pain management specialist. (8)

Regulatory Status
Givlaari® (givosiran) was approved by the U.S. Food and Drug Administration (FDA) on November 20, 2019 for the treatment of adults with acute hepatic porphyria (AHP). (1)

Rationale

Givlaari®
The efficacy of Givlaari in patients with acute hepatic porphyria (AHP) was evaluated in the ENVISION trial (NCT03338816), a randomized, double-blind, placebo-controlled, multinational study.

ENVISION enrolled 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). Eligible patients were randomized 1:1 to receive once monthly subcutaneous injections of Givlaari 2.5 mg/kg or placebo during the 6-month double-blind period. 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. After the 6-month treatment period patients were enrolled in an open label extension period for up to 30 months. Ninety-three patients were enrolled in the open label extension period. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

The median age of patients studied was 37.5 years (range 19 to 65 years), 89% of patients were female, and 78% were white. Givlaari and placebo arms were balanced with respect to historical porphyria attack rate, hemin prophylaxis prior to study entry, use of opioid medications, and patient-reported measures of pain symptoms between attacks.

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.

Efficacy results for Givlaari are provided in Table 1. On average, AHP patients on Givlaari experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo.

Table 1. Rate of Porphyria Attacks[a] and Days of Hemin Use in Patients with AHP Over the 6-Month Double-Blind Period of ENVISION

	Patients with AHP	
	Givlaari (N=48)	**Placebo (N=46)**
Mean Rate (95% CI) of Porphyria Attacks	1.9 (1.3, 2.8)	6.5 (4.5, 9.3)
Rate Ratio[b] (95% CI) (Givlaari/Placebo)	0.3[c] (0.2, 0.4)	

Mean Days (95% CI) of Hemin Use	4.7 (2.8, 7.9)	12.8 (7.6, 21.4)
Ratio[b] (95% CI) (Givlaari/Placebo)	0.3[d] (0.1, 0.5)	

AHP: Acute Hepatic Porphyria.
CI: confidence interval
[a] Attacks that require hospitalization, urgent healthcare visits, or intravenous hemin administration at home.
[b] Adjusted for prior hemin prophylaxis status and historical attack rates. A ratio <1 represents a favorable outcome for Givlaari.
[c] p<0.001
[d] p=0.002

Givlaari also resulted in a reduction of hemin use, urinary ALA (aminolevulinic acid) and urinary porphobilinogen (PBG).

Summary of Evidence
The U.S. Food and Drug Administration (FDA) approved Givlaari®(givosiran) for the treatment of individuals with acute hepatic porphyria (AHP). The FDA approval is based on clinical studies with the following inclusion criteria: Individuals 18 years of age and older; confirmed diagnosis of AHP (i.e., acute intermittent porphyria [AIP], variegate porphyria [VP], hereditary coproporphyria [HCP], delta-aminolevulinic acid dehydratase deficient porphyria [ADP]); and the patient has active disease with at least two documented porphyria attacks within the 6 months prior to initiation (requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home). The safety, efficacy and improvement on health outcomes are demonstrated in the clinical studies therefore, givosiran (Givlaari®) may be considered medically necessary when established criteria are met. Givosiran (Givlaari®) is considered experimental, investigational, and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0223

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2024	Document updated with literature review. Coverage unchanged. No new references added; some updated.
07/01/2023	Reviewed. No changes.

01/15/2023	Document updated with literature review. Coverage unchanged. Reference 8 added, other references updated.
11/01/2021	Reviewed. No changes.
11/15/2020	New medical document. Givosiran (Givlaari™) may be considered medically necessary for the treatment of individuals with acute hepatic porphyria (AHP) who meet the following criteria: individuals 18 years of age and older; and patient has a confirmed diagnosis of acute hepatic porphyria (AHP) [i.e., acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), delta-aminolevulinic acid dehydratase deficient porphyria (ADP)]; and patient has active disease with at least two documented porphyria attacks within the 6 months prior to initiation (requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home). Givosiran (Givlaari™) is considered experimental, investigational, and/or unproven for all other indications.