BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 05/18/23**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 05/16/24**
	CURRENT EFFECTIVE DATE: 07/15/24
	LAST CRITERIA REVISION DATE: 02/15/24
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

GIVLAARI© (givosiran)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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GIVLAARI© (givosiran)

Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Givlaari (givosiran) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist, Hepatologist, or Gastroenterologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of acute hepatic porphyria **AND** confirmation of **ONE** of the following disease subtypes:

   - Acute intermittent porphyria (AIP)
   - Hereditary coproporphyria (HCP)
   - Variegate porphyria (VP)
   - ALA dehydratase-deficiency porphyria (ADP)

4. Individual meets **ALL** of the following:

   - Documented active clinical features associated with acute hepatic porphyria (see Definitions section)
   - Documented elevated urinary aminolevulinic acid (ALA) or elevated porphobilinogen (PBG) as confirmed by laboratory results within the past year
   - **ONE** of the following:

     a. Two or more porphyria attacks within the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration at home
     b. The patient is currently receiving prophylactic hemin treatment due to history of severe or frequent porphyria attacks

5. Individual has received and completed a **liver function test** before initiation of treatment and with continued monitoring of the individual as clinically appropriate

6. Individual does **NOT** have **ANY** of the following:

   - Other forms of porphyria (e.g., porphyria cutanea tarda, erythropoietic protoporphyria, etc.)
   - Liver transplantation
   - Concomitant prophylactic hemin treatment while on Givlaari

7. There are no significant interacting drugs, including concomitant use with sensitive CYP1A2 or CYP2D6 substrates (see Definitions section)

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8. The Attestation for Givlaari Treatment form (see below) has been signed by the physician (or designee).

Initial approval duration: 6 months

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

Required Outcomes Measurements:
Provider submits **documentation** of any missed doses and/or discontinuation of the medication

- **Criteria for continuation of coverage (renewal request):** Givlaari (givosiran) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a hematologist, hepatologist, or gastroenterologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of acute hepatic porphyria **AND** confirmation of one of the following disease subtypes:

   - Acute intermittent porphyria (AIP)
   - Hereditary coproporphyria (HCP)
   - Variegate porphyria (VP)
   - ALA dehydratase-deficiency porphyria (ADP)

4. Individual's condition has responded while on therapy with response defined as **TWO** of the following:

   - A reduction in the rate of porphyria attacks
   - A reduction in hemin requirements for acute attacks since initiating therapy
   - Porphobilinogen (PBG) or delta-aminolevulinic acid (ALA) concentration has decreased from baseline
   - Improvement of signs and symptoms of AHP (i.e., pain, neurovisceral symptoms, gastrointestinal symptoms, renal function improvement, skin lesions, etc.)

5. Individual has been adherent with the medication

6. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:

- Clinically significant transaminase elevations, defined as alanine aminotransferase (ALT) greater than 5 times the upper limit of normal
- Anaphylaxis
- Clinically significant renal toxicity

7. There are no significant interacting drugs, including concomitant use with sensitive CYP1A2 or CYP2D6 substrates (see Definitions section)

8. Individual does **NOT** have **ANY** of the following:

   - Other forms of porphyria (e.g., porphyria cutanea tarda, erythropoietic protoporphyria, etc.)
   - Liver transplantation
   - Concomitant prophylactic hemin treatment while on Givlaari

9. The Attestation for Givlaari Treatment form (see below) has been signed by the physician (or designee). [Note: Signed treatment form only needed once for any treating physician and may not be needed on renewal.]

Renewal duration: 12 months

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

Required Outcomes Measurements:
Provider submits **documentation** of any missed doses and/or discontinuation of the medication

- Givlaari (givosiran) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

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Attestations for Givlaari Treatment

Physician Name: _____

Individual Name: _____ DOB**:** _____

- The Physician is responsible for filling out this form.
- All elements must be initialed, and the form must be signed by the Physician (or designee).
- Incomplete forms will be returned to acquire missing information, initial, signature, or date.
- Return completed form to BCBSAZ.

Physician Agreement:

- Physician to initial by each element and date and sign to show willingness to participate.
- Documentation may include, but is not limited to, chart notes, laboratory test results, claims records, and/or other information.

Initials:

_____ I verify that the patient will be closely followed and monitored for progression of disease

_____ I agree to submit clinical outcomes data and information

_____ I agree to submit documentation if the individual misses a dose OR discontinues the medication

Provider (or designee) Signature: _____

Date: _____

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Description:

Porphyria refers to a class of rare, genetic, metabolic disorders characterized by altered enzymatic activity within the heme biosynthetic pathway and is further defined by a series of disease subclassifications with varying clinical manifestations. The three main manifestations of porphyria include acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), and erythropoietic protoporphyria (EPP). AIP is the most common presentation among a subclass of porphyrias known as acute hepatic porphyria (AHP), which also includes delta-aminolevulinic acid dehydratase porphyria (ADP), hereditary coproporphyria (HCP), and variegate porphyria (VP). Givlaari© is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria.

In patients suffering from one of the four subtypes of acute hepatic porphyria, a causative variant affects the particular gene that encodes for its respective heme synthesis enzyme. In total, eight enzymes work in stepwise fashion to accomplish heme biosynthesis. Specifically, mutations in porphobilinogen deaminase (PBGD), the third enzyme in the heme biosynthetic pathway, cause AIP. Mutations in delta-aminolevulinic acid dehydratase (ALAD), the second enzyme implicated in the heme synthesis pathway, cause the ADP manifestation. The sixth stepwise enzyme responsible for heme synthesis is known as coproporphyrinogen oxidase (CPOX) – mutations in this enzyme are responsible for HCP. VP is caused by mutations in protoporphyrinogen oxidase (PPOX), the seventh enzyme in the pathway.

In all patients with acute hepatic porphyria, upregulation of hepatic ALA synthase 1 (ALAS1) leads to an accumulation of neurotoxic heme intermediates, including ALA and porphobilinogen (PBG). Both ALA and PBG are accumulated in AIP, HCP, and VP, whereas only ALA is shown to accumulate in ADP. In other types of porphyria, ALA and PBG levels are typically shown to be normal.

The resulting accumulation of ALA and/or PBG causes neurotoxicity and organ damage, exemplified by acute attacks and chronic disease manifestations. Presenting signs and symptoms of disease include paralysis, seizure, muscle weakness, pain (especially neuropathic and within the abdominal region), blistering skin lesions, insomnia, agitation, hyponatremia, nausea/vomiting, and constipation. Chronic kidney disease (CKD), hypertension, and liver disease are additional complications that have been associated with AHP as a result of long-term accumulation of PBG and ALA.

Givlaari (givosiran) is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with AHP. It causes degradation of ALAS1 mRNA in hepatocytes through RNA interference, reducing the elevated levels of hepatic ALAS1 mRNA. This subsequently leads to a reduction in circulating levels of neurotoxic heme intermediates, including both ALA and PBG, leading to a decreased frequency of acute attacks.

Currently, for management of acute porphyria attacks, intravenous hemin administration is recommended, often in combination with carbohydrate loading in order to quickly down-regulate ALAS1. When administered intravenously, hemin is partially bound to plasma hemopexin and extensively bound to albumin, allowing for quick reuptake into hepatocytes. FDA-approved dosing guidance for hemin recommends 3-4 mg/kg IV for a period of four days, although in clinical practice, hemin therapy may continue for up to 14 days. Opioid analgesia exists as adjunctive supportive care in instances of acute attack, in addition to the removal of potential triggering factors, such as smoking and alcohol

consumption. Short-term hemin administration is recommended in all suspected cases of acute porphyria attack, regardless of an individual's concurrent maintenance therapy with Givlaari (givosiran).

Prior to the FDA – approval of Givlaari, chronic management and preventative treatment options for AHP included off-label prophylactic hemin administration and, in severe, disabling cases of recurrent AHP attacks, liver transplantation. However, for patients with recurrent AHP attacks, frequent hemin infusion has been associated with long-term venous damage due to the presence of heme degradation products. High dosages of hemin may also lead to overexpression of heme oxygenase 1, which can result in heme degradation and loss of feedback inhibition of ALAS1. Current clinical recommendations do not support concurrent use of Givlaari and prophylactic hemin at this time.

Definitions:

Porphyria:
A group of disorders that result from a buildup of natural chemicals that produce porphyrin in the body.

Heme:
An iron-containing compound of the porphyrin class which forms the nonprotein part of hemoglobin and some other biological molecules.

Clinical Features of AHP:

- Neurovisceral symptoms: Symptoms of, relating to, or affecting the viscera and the autonomic nervous system that innervates them. Examples include abdominal pain, motor and sensory peripheral neuropathy, neuropsychiatric changes (i.e., anxiety, disorientation, agitation, psychosis, seizure, sensory deficits, insomnia), muscle weakness, pain in the arms and legs, systemic arterial hypertension, tachycardia, fever, respiratory paralysis, and urinary retention (due to bladder paresis)
- Cutaneous photosensitivity including blistering skin lesions
- Hepatic involvement, constipation, nausea/vomiting, brownish or reddish urine coloration, and hyponatremia

Potential Drug Interactions

Enzyme or Transporter Mechanism	Potential Interaction with Givlaari©
CYP1A2 substrates (avoid combination or consider therapy modification)	alosetron, bendamustine, pirfenidone, rasagiline, theophylline derivatives, tizanidine
CYP2D6 substrates (avoid combination or consider therapy modification)	doxorubicin, mequitazine, thioridazine, eliglustat, tamoxifen

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History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	05/16/24	Review with revisions: criteria, resources (effective 07/15/24)
Pharmacy and Therapeutics Committee	02/15/24	Revisions to guideline (effective 04/16/24)
Pharmacy and Therapeutics Committee	11/16/23	Revisions to guideline (effective 01/15/24)
Pharmacy and Therapeutics Committee	05/18/23	Reviewed and approved policy
Clinical Pharmacist	03/10/23	Development

Coding:

HCPCS: J0223

GIVLAARI© (givosiran)

Resources:

Literature reviewed 05/16/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Anderson KE. Acute hepatic porphyrias: Current diagnosis & management. *Mol Genet Metab*. 2019; 128(3):219-227. doi:10.1016/j.ymgme.2019.07.002

2. Anderson KE, Porphyrias: An overview. In: UpToDate, Means, RT, Tirnauer, JS, et al. (Eds), UpToDate, Waltham, MA. Available at https://uptodate.com. Topic last updated March 11, 2022. Accessed February 16, 2024.

3. Balwani M, Sardh E, Ventura P, et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. NEJM 2020; 382(20):1289-2301. doi:10.1056/NEJMoa1913147

4. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. *Hepatology*. 2017; 66(4):1314-1322. doi:10.1002/hep.29313

5. Givlaari© (givosiran) product information revised by Alnylam Pharmaceuticals, Inc. 02/2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 16, 2024.

6. Sood GK, Anderson KE, Acute intermittent porphyria: Management. In: UpToDate, Means, RT, Tirnauer, JS, et al. (Eds), UpToDate, Waltham, MA. Available at https://uptodate.com. Topic last updated March 14, 2022. Accessed February 16, 2024.

7. Sood GK, Anderson KE, Acute intermittent porphyria: Pathogenesis, clinical features, and diagnosis. In: UpToDate, Means, RT, Tirnauer, JS, et al. (Eds), UpToDate, Waltham, MA. Available at https://uptodate.com. Topic last updated June 1, 2022. Accessed February 16, 2024.

8. Stölzel U, Doss MO, Schuppan D. Clinical Guide and Update on Porphyrias. *Gastroenterology.* 2019; 157(2): 365-381. doi: 10.1053/j.gastro.2019.04.050

9. Wang B, Rudnick S, Cengia B, et al. Acute Hepatic Porphyrias: Review and Recent Progress. *Hepatol Commun*. 2018; 3(2):193-206. doi:10.1002/hep4.1297

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Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html