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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Hematological Agents	**Original Policy Date:**	December 13, 2019
Subject:	Givlaari	**Page:**	1 of 5

Last Review Date: December 8, 2023

Givlaari

Description

Givlaari (givosiran)

Background
Givlaari (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 acute hepatic porphyria (AHP) (1).

Regulatory Status
FDA-approved indication: Givlaari is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP) (1).

A healthcare professional must be available to administer the subcutaneous injection in order to accurately determine the weight-based dosage and be able to appropriately manage anaphylactic reactions if necessary when administering Givlaari (1).

Givlaari should be monitored for increases in transaminase elevations (ALT). Initially, prescribers should measure liver function tests prior to beginning treatment with Givlaari, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Prescribers should also monitor renal function during treatment for increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) (1).

The safety and effectiveness of Givlaari in pediatric patients have not been established (1).

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Givlaari may be considered **medically necessary** if the conditions indicated below are met.

Givlaari may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Acute hepatic porphyria (AHP)

AND ALL of the following:

1. AHP diagnosis has been confirmed by **ALL** of the following:
    a. Elevated porphobilinogen (PBG) **OR** delta-aminolevulinic acid (ALA) concentration
    b. Genetic confirmation of **ONE** of the following:
        i. Hydroxymethylbilane synthase (HMBS)
        ii. Coproporphyrinogen oxidase (CPOX)
        iii. Protoporphyrinogen oxidase (PPOX)
        iv. ALA dehydratase (ALAD)
2. Patient has **ONE** of the following:
    a. Active, symptomatic disease with at least two documented porphyria attacks requiring acute care within the last 6 months
    b. Currently receiving prophylactic hemin treatment due to a history of severe or frequent porphyria attacks

3. Baseline urinary or plasma porphobilinogen (PBG) or delta-aminolevulinic acid (ALA) concentrations have been obtained
4. Patient will **NOT** be receiving concurrent use of prophylactic hemin treatment
5. Prescriber agrees to monitor liver function tests (LFTs)
6. Prescriber agrees to monitor renal function

Prior–Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Acute hepatic porphyria (AHP)

AND ALL of the following:

1. Patient has had a clinical response to therapy as demonstrated by **ONE** of the following:
    a. A reduction in the rate of porphyria attacks
    b. A reduction in hemin requirements for acute attacks
2. Porphobilinogen (PBG) or delta-aminolevulinic acid (ALA) concentration has not increased from baseline
3. Prescriber agrees to monitor liver function tests (LFTs)
4. Prescriber agrees to monitor renal function

Policy Guidelines

Pre–PA Allowance

None

Prior–Approval Limits

Duration 12 months

Prior–Approval *Renewal* Limits

Duration 12 months

Rationale

Summary
Givlaari (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 (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Givlaari while maintaining optimal therapeutic outcomes.

References
1. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; February 2023.

Policy History

Date	Action
December 2019	Addition to PA
March 2020	Annual review. Added initiation requirements: patient has active, symptomatic disease with at least two porphyria attacks requiring acute care in last 6 months; AHP diagnosis confirmed by elevated tests or genetic mutation; and baseline PBG or ALA concentration. Also added continuation requirement of no increase in PBG or ALA concentration per SME
June 2021	Annual review and reference update
June 2022	Annual review and reference update

August 2022	Per FEP: revised policy to align with BCBS Association policy: AHP diagnosis requirements were changed to require BOTH elevated PBG or ALA and genetic confirmation of one gene; requirement of active disease changed to allow a patient currently receiving prophylactic hemin treatment due to a history of severe or frequent attacks; added requirement patient will not use concurrently with prophylactic hemin treatments; Continuation requirements revised to include a reduction in hemin requirements for acute attacks since initiating therapy.
September 2022	Annual review and reference update
June 2023	Annual review and reference update
September 2023	Association policy alignment: removed requirement for healthcare provider administration and changed initiation duration to 12 months
December 2023	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.