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Section:	Prescription Drugs	**Effective Date:**	July 1, 2022
Subsection:	Hematological Agents	**Original Policy Date:**	December 13, 2019
Subject:	Givlaari	**Page:**	1 of 4

Last Review Date: June 16, 2022

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** in patients that are 18 years of age and older for the treatment of acute hepatic porphyria and if the conditions indicated below are met.

Givlaari may be considered **investigational** in patients under 18 years of age and 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 **ONE** 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 active, symptomatic disease with at least two documented porphyria attacks requiring acute care within the last 6 months
3. Baseline urinary or plasma porphobilinogen (PBG) or delta-aminolevulinic acid (ALA) concentrations have been obtained

4. A healthcare professional will be available to administer medication and give medical support for anaphylactic reactions if necessary
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. Reduction in the rate of porphyria attacks since initiating therapy
2. Porphobilinogen (PBG) or delta-aminolevulinic acid (ALA) concentration has not increased from baseline
3. A healthcare professional will be available to administer medication and give medical support for anaphylactic reactions if necessary
4. Prescriber agrees to monitor liver function tests (LFTs)
5. Prescriber agrees to monitor renal function

Policy Guidelines

Pre–PA Allowance

None

Prior–Approval Limits

Duration 6 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.; October 2021.

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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 16, 2022 and is effective on July 1, 2022.