Clinical Policy: Givosiran (Givlaari)

Reference Number: PA.CP.PHAR.457
Effective Date: 10/2020
Last Review Date: 01/2025

Description
Givosiran (Givlaari®) is an aminolevulinate synthase 1-directed small interfering RNA.

FDA Approved Indication(s)
Givlaari is indicated for the treatment of adults with acute hepatic porphyria (AHP).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Givlaari is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Acute Hepatic Porphyria (must meet all)**:**

1. Diagnosis of AHP (i.e., acute intermittent porphyria [AIP], hereditary coproporphyria [HCP], variegate porphyria [VP], or ALA dehydratase-deficiency [ALAD] porphyria) confirmed by one of the following (a or b):
   a. Genetic testing (i, ii, iii, or iv):
      i. AIP: positive HMBS (aka PBGD) mutation;
      ii. HCP: positive CPOX mutation;
      iii. VP: positive PPOX mutation;
      iv. ALAD porphyria: positive ALAD mutation;
   b. History of at least a four-fold increase of 5-aminolevulinic acid (ALA) or porphobilinogen (PBG) using a random urine sample within the past year (see Appendix E);
2. Prescribed by or in consultation with a gastroenterologist, hematologist, hepatologist or neurologist;
3. Age ≥ 18 years;
4. History of ≥ 2 porphyria attacks in a 6-month period requiring hospitalization, urgent healthcare visit, or intravenous Panhematin®* (hemin for injection) administration at home, and one of the following (a or b):
   a. The porphyria attacks occurred within the last 6 months;
   b. The porphyria attacks occurred in any 6-month period and member is currently receiving prophylactic Panhematin therapy (e.g., once or twice a week on a regular basis);

   **Prior authorization may be required.*
5. Panhematin, as a prophylactic treatment, is not prescribed concurrently with Givlaari (note: use of Panhematin for treatment of acute porphyria attacks while taking Givlaari is appropriate);
6. Documentation of member's current body weight (in kg);

7. Dose does not exceed 2.5 mg/kg once monthly.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Acute Hepatic Porphyria (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by an improvement of signs and/or symptoms;
3. Documentation of member's current body weight (in kg);
4. If request is for a dose increase, new dose does not exceed 2.5 mg/kg once monthly.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AHP: acute hepatic porphyria
AIP: acute intermittent porphyria
ALA: 5-aminolevulinic acid
ALAD: ALA dehydratase-deficiency
FDA: Food and Drug Administration
HCP: hereditary coproporphyria
PBG: porphobilinogen
VP: variegate porphyria

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Panhematin (hemin for injection)	AIP	6 mg/kg of hematin in any 24 hour period

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	1 to 4 mg/kg/day of hematin for 3 to 14 days based on the clinical signs. Standard dose in clinical practice per the package insert is 3 to 4 mg/kg/day - in more severe cases this dose may be repeated every 12 hours.	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): severe hypersensitivity to Givlaari; reactions have included anaphylaxis.
- Boxed warning(s): none reported.

Appendix D: Porphyria Laboratory and Genetic Testing Resources (not all inclusive)

- Mayo Medical Laboratories (Rochester, MN)
- University of Texas Medical Branch at Galveston - Porphyria Research Center (Galveston, TX)
- Department of Genetics, Icahn School of Medicine - Mount Sinai Porphyria Comprehensive Diagnostic and Treatment Center (New York, NY)
- Invitae (San Francisco, CA)
- LabCorp (Burlington, NC)

Appendix E: ALA and PBG Laboratory Testing

Concentrations of ALA or PBG in a random urine sample greater than four times the upper limit of normal establish the diagnosis of AHP (Wang 2019). Variations in reference ranges and reporting (e.g., with or without creatinine correction) may differ across U.S. laboratories; however, four times the upper limit of normal based on a random urine sample remains an appropriate evaluative tool.

Examples of laboratory reporting variations:*

**ALA/PBG values below are chosen for demonstration purposes only and do not reflect actual required values.*

- Corrected for creatinine:*
  **Additional units applicable here include mg/mmol creatinine.*
  - ALA = 38 mg/g creatinine (reference range 0-7 mg/g creatinine);
  - PBG = 85 mg/g creatinine (reference range 0-4 mg/g creatinine).

  See Wang et al (2019) for additional information.
- Uncorrected for creatinine:*
  **Additional units applicable here include mcmol/L.*
  - ALA = 40 mg/L (reference range 0.0-5.4 mg/L);
  - PBG = 90 mg/L (reference range 0.0-2.0 mg/L).

  See LabCorp (www.labcorp.com) and Mayo Medical Laboratories (www.mayoclinicalabs.com) testing information for additional information.

Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. Hepatology Communications, 2019; 3(2): 193:206.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
AHP	2.5 mg/kg once monthly by subcutaneous injection Missed dose: Administer Givlaari as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose. Dose modification for adverse reactions: • In patients with severe or clinically significant transaminase elevations, who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. • In patients who resume dosing at 1.25 mg/kg once monthly without recurrence of severe or clinically significant transaminase elevations, the dose may be increased to the recommended dose of 2.5 mg/kg once monthly.	2.5 mg/kg/month

VI. Product Availability

Single-dose vial: 189 mg/mL

VII. References

1. Givlaari Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; April 2024. Available at: https://www.givlaari.com. Accessed October 21, 2024.
2. Balwani M, Sardh E, Ventura P, et al. Phase 3 Trial of RNAi Therapeutic givosiran for acute intermittent porphyria. *N Eng J Med.* 2020; 382(24): 2289-2301.
3. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. Hepatology Communications, 2019; 3(2): 193:206.
4. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: Recommendations for evaluation and long term management. *Hepatology*. 2017 October; 66(4): 1322. doi:10.1002/hep.29313.
5. Acute hepatic porphyrias. National Organization for Rare Disorders. Available at https://rarediseases.org/?s=acute+hepatic+porphyria&submit=. Accessed November 14, 2024.
6. Woolf J, Marsden JT, Degg T, et al. Best practice guidelines on first-line laboratory testing for porphyria. *Annals of Clinical Biochemistry*. 2017; 54(2): 188-198.
7. Anderson KE. Acute hepatic porphyrias: current diagnosis and management. *Mol Genet Metab*. 2019 Nov;128(3):219-227. doi: 10.1016/j.ymgme.2019.07.002.
8. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med*. 2005; 142:439-450.

9. Wang B, Bonkovsky HL, Lim JK, and Balwani M. AGA Clinical practice update on diagnosis and management of acute hepatic porphyrias: Expert review. Gastroenterology 2023;164:484-491.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0223	Injection, givosiran, 0.5 mg

Reviews, Revisions, and Approvals	Date
Policy created.	10/2020
1Q2021 annual review: no significant changes; references reviewed and updated.	01/2021
1Q 2022 annual review: clarified that ALA/PBG urine sample must be recent (within the past year); references reviewed and updated.	01/2022
1Q 2023 annual review: no significant changes; added hepatologist as specialty able to prescribe or be in consultation with; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; added criteria "documentation of member's current body weight (in kg);" references reviewed and updated.	01/2024
1Q 2025 annual review: no significant changes; references reviewed and updated.	