Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 02/01/2022**
Policy Number: PA.CP.PHAR.457	**Effective Date: 10/2020** **Revision Date: 01/2022**
Policy Name: Givosiran (Givlaari)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

1Q 2022 annual review: clarified that ALA/PBG urine sample must be recent (within the past year); references reviewed and updated.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

Clinical Policy: Givosiran (Givlaari)

Reference Number: PA.CP.PHAR.457
Effective Date: 10/2020
Last Review Date: 01/2022

Coding Implications
Revision Log

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 health plans affiliated with 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 one of the following AHP subtypes with confirmatory genetic testing (a, b, c, or d):
   a. Acute intermittent porphyria (AIP) and a positive HMBS (aka PBGD) mutation;
   b. Hereditary coproporphyria (HCP) and a positive CPOX mutation;
   c. Variegate porphyria (VP) and a positive PPOX mutation;
   d. ALA dehydratase-deficiency (ALAD) porphyria and a positive ALAD mutation;
2. Prescribed by or in consultation with a gastroenterologist, hematologist, or neurologist;
3. Age ≥ 18 years;
4. 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*);
5. 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 (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.*
6. 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);
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.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy as evidenced by an improvement of signs and/or symptoms;
3. 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.LTSS.PHAR.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 for all relevant lines of business and may require prior authorization.

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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	2.5 mg/kg/month

Indication	Dosing Regimen	Maximum Dose
	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.	

VI. Product Availability

Single-dose vial: 189 mg/mL

VII. References

1. Givlaari Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; December 2020. Available at: https://www.givlaari.com. Accessed October 18, 2021.
2. Panhematin Prescribing Information. Raleigh, NC: Xelia Pharmaceuticals USA, LLC; May 2020. Available at https://www.panhematin.com. Accessed October 18, 2021.
3. 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.
4. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. Hepatology Communications, 2019; 3(2): 193:206.
5. 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.
6. Acute hepatic porphyrias. National Organization for Rare Disorders. Available at https://rarediseases.org/?s=acute+hepatic+porphyria&submit=. Accessed October 18, 2021.
7. 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.
8. 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.
9. 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.

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