Clinical Policy: Givosiran (Givlaari)

Reference Number: ERX.SPA.374
Effective Date: 03.01.20
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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, 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 (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. Dose does not exceed 2.5 mg/kg once monthly.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. Decreased number of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous Panhematin administration at home;
   b. No increase in porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous Panhematin administration at home if member was receiving prophylactic Panhematin therapy prior to Givlaari initiation;
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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

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 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.	6 mg/kg of hematin in any 24 hour period

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.; 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	01.14.20	02.20
Corrected-for-creatinine requirement removed from diagnostic porphyrin precursor (ALA/PBG) testing criteria to reflect lab reporting variability; examples of ALA/PBG values, uncorrected for creatinine, are added to Appendix E; references reviewed and updated.	07.07.20	08.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	10.20.20	02.21
1Q 2022 annual review: revised confirmatory diagnostic criteria from requiring both genetic testing and ALA/PBG to either genetic testing or elevated ALA/PBG as some AHP patients do not have identifiable mutations; clarified that ALA/PBG urine sample must be recent (within the past year); references reviewed and updated.	01.05.22	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.