

Clinical Policy: Givosiran (Givlaari)

Reference Number: CP.PHAR.457

Effective Date: 03.01.20

Last Review Date: 02.20

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)

[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.

It is the policy of health plans affiliated with Centene Corporation[®] 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 \geq 18 years;
4. History of at least a four-fold increase of 5-aminolevulinic acid (ALA) or porphobilinogen (PBG) measured as mg/g creatinine using a random urine sample (*see Appendix E*);
5. History of \geq 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:

Medicaid/HIM – 6 months

Commercial – 6 months or to the member’s renewal date, whichever is longer

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Acute Hepatic Porphyria (must meet all):

1. Currently receiving medication via Centene benefit 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:

Medicaid/HIM – 12 months

Commercial – 6 months or to the member’s renewal date, whichever is longer

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.**

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AHP: acute hepatic porphyria	FDA: Food and Drug Administration
AIP: acute intermittent porphyria	HCP: hereditary coproporphyria
ALAD: ALA dehydratase-deficiency	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 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 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)

Appendix E: ALA and PBG Laboratory Testing

Levels of ALA and/or PBG, expressed as mg per gram or millimole creatinine in a random urine sample, that are greater than four times the upper limit of normal establish the diagnosis of AHP (e.g., ALA = 38 mg/g creatinine [reference range 0-7] or PBG = 85 mg/g creatinine [reference range 0-4]). Normal ranges may differ among U.S. laboratories based on testing methodology.

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	<p>2.5 mg/kg once monthly by subcutaneous injection</p> <p><u>Missed dose:</u> Administer Givlaari as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose.</p> <p><u>Dose modification for adverse reactions:</u></p> <ul style="list-style-type: none"> • 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.; November 2019. Available at: <https://www.alnylam.com/wp-content/uploads/pdfs/GIVLAARI-Prescribing-Information.pdf>. Accessed December 9, 2019.
2. Givlaari Patient Brochure. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; November 2019. Available at: <https://www.alnylamassist.com/sites/default/files/pdfdownloads/GIVLAARI-givosiran-Patient-Brochure.pdf>. Accessed December 9, 2019.
3. Givlaari Drug Approval Package - Multi-Discipline Review, Application Number 212194. Food and Drug Administration Center for Drug Evaluation and Research. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212194Orig1s000TOC.cfm. Accessed December 17, 2019.
4. Panhematin Prescribing Information. Raleigh, NC: Xelia Pharmaceuticals USA, LLC; July 2017. Available at <https://www.panhematin.com/pdf/panhematin-marketing-PI.pdf>. Accessed December 17, 2019.

Givlaari Pivotal Trial Abstracts

5. Gouya L, Sardh E, Balwani M, et al. ENVISION, a phase 3 study to evaluate the efficacy and safety of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1, in acute hepatic porphyria patients. Presented at: The International Congress on Porphyrins and Porphyrrias, Milan, Italy. September 10, 2019.
6. Balwani M, et al. ENVISION, a phase 3 study to evaluate the efficacy and safety of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1, in acute hepatic porphyria patients. Presented at: The International Liver Congress, Vienna, Austria. April 13, 2019.

Porphyria Guidelines

7. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. *Hepatology Communications*, 2019; 3(2): 193:206.
8. 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.
9. Acute hepatic porphyrias. National Organization for Rare Disorders. Available at <https://rarediseases.org/?s=acute+hepatic+porphyria&submit=>. Accessed December 17, 2019.
10. 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.
11. 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
TBD	TBD

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	01.14.20	02.20

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2020 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.