



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 02/08/2024

Givlaari® (givosiran)

HCPCS: J0223

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Coverage of the requested drug is provided when all the following are met:
 - a. FDA approved age
 - b. Diagnosis of Acute Hepatic Porphyria (AHP) which includes: ALA-Dehydratase Deficiency Porphyria (ADP), Acute Intermittent Porphyria (AIP), Hereditary Coproporphyrinuria (HCP), or Variegate Porphyria (VP)
 - c. Documentation of elevated urinary aminolevulinic acid (ALA) OR porphobilinogen (PBG) levels above the lab test upper limit of normal obtained during an acute attack AND/OR genetic testing positive for a mutation consistent with ADP, AIP, HCP, or VP
 - d. Have active disease with at least 2 documented porphyria attacks in the last 6 months OR chronic baseline disease activity with symptoms such as:
 - i. Pain in the abdomen, back, and/or chest
 - ii. Cardiovascular conditions including hypertension and tachycardia
 - iii. Gastrointestinal involvement including nausea, vomiting, and constipation
 - iv. Neurological involvement including neuropathic pain, sensory loss, muscle weakness, paralysis, confusion, anxiety, depression, memory loss, fatigue, hallucinations, seizures
 - v. Other system involvement including respiratory failure, skin lesions, hyponatremia
 - e. Have taken the appropriate lifestyle modifications to prevent acute attacks including, but not limited to: dietary modifications, quitting smoking, stopping alcohol use, and removing medications known to cause acute attacks when possible
 - f. Must not have had a previous liver transplant or have a scheduled liver transplant
 - g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.
- B. Quantity Limitations, Authorization Period and Renewal Criteria
 - a. Quantity Limits: Align with FDA recommended dosing
 - b. Authorization Period: One year at a time
 - c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Acute Hepatic Porphyria (AHP) is a rare, autosomal dominant disorder with 4 different variations (Acute Intermittent Porphyria, Hereditary Coproporphyrin, Variegate Porphyria, and ALA Dehydratase-Deficient Porphyria) that results from a partial deficiency in 4 enzymes that are part of the heme biosynthetic pathway leading to an accumulation of toxic heme intermediaries, aminolevulinic acid (ALA) and porphobilinogen (PBG), which are thought to cause the clinical manifestations of AHP.
- An estimated 5,000 patients in the US and Europe suffer from AHP attacks annually, and 500 to 1,000 experience recurrent attacks. The incidence and prevalence of AHP in Sweden is 4 times as high compared to the rest of Europe.
- Signs and symptoms of AHP are generally nonspecific and typically occur as intermittent acute attacks that are sometimes life-threatening. The most common symptoms include abdominal pain, vomiting, constipation, muscle weakness, psychiatric symptoms, hypertension, painful urination, and urinary retention or incontinence. Acute attacks are usually associated with exacerbating factors, such as medications, smoking, sex hormones, fasting and stress.
- Most patients have a complete resolution in their symptoms between attacks; however, some patients develop chronic symptoms including pain requiring opioid analgesics, depression/anxiety, and persistent hypertension.
- The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network (2017) guidelines provide the following recommendations for long-term management of AHP:
 - Management should focus on the identification and avoidance of factors that precipitate or worsen acute AHP attacks. Patients should be counseled to avoid certain environmental triggers, including certain medications, crash dieting or fasting-type dieting, smoking (tobacco and marijuana), and alcohol.
 - Prophylactic therapy with hemin or intravenous glucose can decrease ALAS-1 activity after 2-3 infusions, with hemin having a more potent effect. Hemin is often used for more severe attacks while glucose loading is used for only mild attacks with improvement in symptoms generally seen within 3-4 days. Patients who experience four or more attacks per year may require hemin prophylaxis up to twice weekly; however, some patients do report improvement with monthly infusions.
 - Severe iron overload can occur with recurrent heme administration leading to the necessity of therapeutic phlebotomy when ferritin levels are >1000 ng/mL.
 - Supportive therapy to address symptoms of AHP may be needed, including pain medications (such as opioids), electrolyte replacement, anticonvulsants, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and calcium channel blockers.
 - Liver transplantation is a last-line option for AHP which has been shown to be curative; however, due to significant morbidity and mortality associated with liver transplantation, this surgical procedure is reserved for those with severe, disabling, intractable attacks that are refractory to hemin therapy.

- Clinical trials assessing Givlaari as treatment in AHP were ongoing at the time of publication of the Porphyria Consortium's guidelines (2017); therefore, current guidelines do not include recommendations for Givlaari in the setting of AHP.
- The American Gastroenterological Association (AGA) Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review (2023) provides additional recommendations regarding the diagnosis and management of AHP including the following Best Practice Statements:
 - Initial diagnosis of AHP should be made by biochemical testing measuring ALA, PBG, porphyrins, and creatinine in a random urine sample.
 - Genetic testing should be used to confirm the diagnosis of AHP in patients with positive biochemical testing.
 - Prophylactic heme therapy or givosiran, administered in an outpatient setting, should be considered in patients with recurrent attacks (4 or more per year).
- Givlaari (givosiran) is the first and only FDA-approved therapy for the treatment of adults with AHP. Givlaari is a double-stranded small interfering RNA (siRNA) which acts in the liver to reduce circulating levels of neurotoxic intermediaries, ALA and PBG.
- Givlaari was evaluated in a Phase III, double-blind, placebo-controlled trial (ENVISION, NCT03338816), which enrolled 94 patients ages 12 years of age and older with symptomatic AHP and at least 2 documented porphyria attacks within the last 6 months. Of the 94 patients enrolled in the trial, 89 had Acute Intermittent Porphyria, 1 had Hereditary Coproporphyrin, 2 had Variegate Porphyria, and 2 had Acute Hepatic Porphyria without an identified mutation.
 - Methods: Patients were randomized to receive once monthly injections of either subcutaneous Givlaari at a dose of 2.5 mg/kg (N=48) or placebo (N=46) for a total of 6 months.
 - Endpoints: The primary endpoint was reduction relative to placebo in the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria (the most common subtype of AHP), defined as attacks requiring hospitalization, an urgent healthcare visit, or hemin administration. Key secondary endpoints included evaluation of ALA and PGP levels in addition to hemin use in patients with Acute Intermittent Porphyria.
 - Results:
 - Primary endpoint: In patients with Acute Intermittent Porphyria, the average annualized rate of composite porphyria attacks over 6 months was 3.2 (95% CI: 2.3 – 4.6) in the Givlaari group compared to 12.5 (95% CI: 9.4 – 16.8) in the placebo group, representing a 74% lower rate of averaged annualized attacks for the Givlaari group ($p < 0.001$). Results were similar for patients with other subtypes of AHP.
 - Secondary endpoints: Among patients with Acute Intermittent Porphyria, treatment with Givlaari led to significantly lower levels of urinary ALA and PGP and fewer days of hemin use (6.8 days v. 29.7 days) compared to the placebo.

References:

1. Givlaari® [package insert]. Alnylam Pharmaceuticals, Inc.; Cambridge, MA, November 2019.
2. Panhematin® [package insert]. Sagent Pharmaceuticals, Inc.; Lebanon, NJ, May 2020.
3. Balwani M, Sardh E, Ventura P, et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147
4. Ramanujam VS, Anderson KE. Porphyria Diagnostics-Part 1: A Brief Overview of the Porphyrias. *Curr Protoc Hum Genet*. 2015;86:17.20.1–17.20.26.
5. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. *Hepatology*. 2017;66(4):1314–1322.
6. Bonkovsky HL, Rudnick SR. Acute Porphyrias. Merck Manuals Professional Version. 2019. [Accessed on December 21, 2022 from <https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/porphyrias/acute-porphyrias>].
7. The Porphyrias Consortium. Rare Clinical Diseases Research Network: National Institutes of Health. [Accessed on December 21, 2022 from <https://www.rarediseasesnetwork.org/cms/porphyrias>].
8. Wang B, Rudnick S, et al. Acute Hepatic Porphyrias: Review and Recent Progress. *Hepatology Communications*. 2019; 3:193-206.
9. Porphyria. U.S. National Library of Medicine Genetics Home Reference. 2019. [Accessed on January 4, 2012 from <https://ghr.nlm.nih.gov/condition/porphyria>].
10. Porphyria (Acute) Testing Algorithm. Mayo Clinic Laboratories. [Accessed on December 21, 2022 from https://www.mayocliniclabs.com/it-mmfiles/Porphyria_Acute_Testing_Algorithm.pdf].
11. Press Release: Alnylam Announces Approval of GIVLAARI™ (givosiran) by the U.S. Food and Drug Administration (FDA). November 20, 2019. [Accessed on December 21, 2022 from <https://www.businesswire.com/news/home/20191120005849/en/>].
12. Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review. *Gastroenterology*. 2023;164(3):484-491.

Policy History												
#	Date	Change Description										
1.6	Effective Date: 02/08/2024	Updated to remove the specialist prescriber requirement and change the renewal criteria to standard language										
1.5	Effective Date: 02/03/2023	Annual review of criteria was performed, no changes were made										
1.4	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made										
1.3	Effective Date: 02/04/2021	Annual review of criteria was performed, no changes were made										
1.2	Effective Date: 06/01/2020	UM medical management system update for MAPPO and BCNA <table border="1" data-bbox="483 564 1365 774"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
BCN	Yes											
MAPPO	Yes											
BCNA	Yes											
1.1	Effective Date: 03/01/2020	UM medical management system update for BCBS <table border="1" data-bbox="483 850 1365 1060"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
BCN	Yes											
MAPPO	No											
BCNA	No											
1.0	Effective Date: 02/06/2020	New full drug review . UM medical management system update for BCN <table border="1" data-bbox="483 1136 1365 1346"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	No
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	No											
BCN	Yes											
MAPPO	No											
BCNA	No											

* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form
Givlaari™ (givosiran) HCPCS CODE: J0223



This form is to be used by participating physicians to obtain coverage for Givlaari. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	Name
ID Number	Specialty
D.O.B. <input type="checkbox"/> Male <input type="checkbox"/> Female	Address
Pt weight (in kg) Date recorded: _____	City /State/Zip
Diagnosis	Phone/Fax: P: () - F: () -
Drug Name	NPI
Dose and Quantity	Contact Person
Directions	Contact Person Phone / Ext.
Date of Service(s)	

STEP 1: DISEASE STATE INFORMATION

1. Initiation or Continuation of treatment? Initiation Continuation *Date patient started therapy:* _____
2. Site of administration? Provider office/Home infusion Other: _____
 Hospital outpatient facility (go to #3) *Reason for Hospital Outpatient administration:* _____
3. Please specify location of administration if hospital outpatient infusion: _____
4. Please provide the NPI number for the place of administration: _____
5. Is Givlaari prescribed by or in consultation with a physician that has experience managing acute hepatic porphyria? Yes No *Comment:* _____
6. **Initiation AND Continuation of Therapy:**
 - a. Please check the patient's diagnosis:
 - i. Acute hepatic porphyria (AHP)
 1. Does AHP include any of the following?
 ALA-Dehydratase Deficiency Porphyria (ADP) Acute Intermittent Porphyria (AIP) Hereditary Corproporphyria (HCP)
 Variegate Porphyria (VP) Other
 - ii. Other: _____
 - b. How has the patient been diagnosed with AHP? (*labs are required*)
 Elevated urinary aminolevulinic acid (ALA): _____ μmol/L *Date:* _____
 Porphobilinogen (PBG) levels above the lab tests upper level of normal obtained during an acute attack: _____ μmol/L *Date:* _____
 Genetic testing positive for a mutation consistent with ADP, AIP, HCP, or VP: _____ *Date:* _____
 Other
 - c. Does the patient have active disease with at least 2 documented porphyria attacks in the last 6 months? Yes No *Comment:* _____
 - d. Does the patient have chronic baseline disease activity with symptoms such as:
 Pain in the abdomen, back, and/or chest Cardiovascular conditions including hypertension, and tachycardia
 Gastrointestinal involvement including nausea, vomiting, and constipation
 Neurological involvement including neuropathic pain, sensory loss, muscle weakness, paralysis, confusion, anxiety, depression, memory loss, fatigue, hallucinations, seizures
 Other system involvement including respiratory failure, skin lesions, hyponatremia
 - e. Has the patient taken the appropriate lifestyle modifications to prevent acute attacks including but not limited to: dietary modifications, quitting smoking, stopping alcohol use, and removing medications known to cause acute attacks when possible? Yes No
 - f. Has the patient had a previous liver transplant or an anticipated liver transplant? Yes No
7. **Continuation request:** Givlaari start date _____
 - a. Has the patient had a reduction in the number of AHP attacks or baseline symptoms of AHP since starting therapy?
 Yes No *Comment:* _____
 - b. Has the patient received a liver transplant since starting Givlaari? Yes No

Please add any other supporting medical information necessary for our review

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	Physician Signature	Date
Step 2: Checklist	<input type="checkbox"/> Form Completely Filled Out <input type="checkbox"/> Attached Chart Notes	<input type="checkbox"/> Weight (specify lb or kg)
Step 3: Submit	By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979	By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320

Confidentiality notice: This transmission contains confidential information belonging to the sender that is legally privileged. This information is intended only for use of the individual or entity named above. The authorized recipient of this information is prohibited from disclosing this information to any other party. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or action taken in reliance on the contents of this document is strictly prohibited. If you have received this in error, please notify the sender to arrange for the return of this document.