Medical Policy Bulletin

Title:
Givosiran (Givlaari) and Panhematin (Hemin)
Policy #:
MA08.112a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

GIVOSIRAN (GIVLAARI)
Initial Therapy

Initiation of givosiran (Givlaari) is considered medically necessary and, therefore, covered if the following criteria are met:

- The individual is 18 years of age or older
- The individual has a diagnosis of acute hepatic porphyria (AHP), and confirmation of one of the following subtypes:
    - Acute intermittent porphyria (AIP)
    - Hereditary coproporphyria (HCP)
    - Variegate porphyria (VP)
    - Aminolevulinic acid dehydratase–deficiency porphyria (ADP)
- The individual has documentation of elevated urinary or plasma porphobilinogen (PBG) or delta-ALA within the past year
- The individual meets one of the following criteria:

- Has active symptomatic disease, with at least two documented porphyria attacks within the past 6 months
- Is currently on prophylactic hemin treatment due to history of severe or frequent porphyria attacks

Dosing and Frequency

The recommended dosing for givosiran (Givlaari) by the US Food and Drug Administration (FDA) is 2.5 mg/kg given subcutaneously (SC) once every month by a healthcare provider. The injections must be administered in a facility that is equipped and staffed to handle any anaphylactic reactions that may occur.

Continuation Therapy

Continuation of givosiran (Givlaari) is considered medically necessary and, therefore, covered if the following criteria are met:

- The individual has experienced a clinical response to therapy (e.g., a reduction in the number of porphyria attacks, or a reduction in hemin requirements for acute attacks)
- The individual does not have severe or clinically significant transaminase elevations, defined as alanine aminotransferase (ALT) greater than five times the upper limit of normal.

Evio has been selected by the Company to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies. Givosiran (Givlaari) is included in the portfolio of high-cost drug therapies for which Evio will be tracking clinical outcomes. If a patient meets all medical policy provisions and is approved to receive treatment, the requesting professional provider or member must attest and agree to providing clinical outcomes data and information via Evio's secure web portal as requested.

PANHEMATIN (HEMIN)

Panhematin (Hemin) is considered medically necessary and, therefore, covered for individuals with AHP when all of the following criteria are met:

- The individual is 16 years of age or older
- The individual has a diagnosis of AHP, and confirmation of one of the following subtypes:
  - Acute intermittent porphyria (AIP)
  - Hereditary coproporphyria (HCP)
  - Variegate porphyria (VP)
  - ALA dehydratase-deficiency porphyria (ADP)
- The individual has documentation of elevated urinary or plasma PBG, delta-aminolevulinic acid (ALA), or total porphyrin prior to receiving treatment
- The individual has presence of clinical symptoms suggestive of an acute porphyric attack (e.g., unremitting abdominal pain, neuropathy, paresis, tachycardia)

If the individual has recurrent porphyria attacks (≥4 per year), prophylactic use of panhematin (Hemin)—with or without the presence of symptoms—is considered medically necessary.

Dosing and Frequency

The recommended dosing for panhematin (Hemin) is 1 to 4 mg/kg/d intravenous (IV) for 3 to 14 days based on the clinical signs. In more severe cases, this dose may be repeated no earlier than every 12 hours.

EXPERIMENTAL/INVESTIGATIONAL

Givosiran (Givlaari) is considered experimental/investigational and, therefore, not covered for the following:

- For concurrent use of prophylactic panhematin (Hemin) treatment with givosiran; OR
- When liver transplantation is anticipated; OR
- When an individual has a history of recurrent pancreatitis; OR

- When an individual is requesting for other forms of porphyria, such as cutaneous porphyrias (e.g., porphyria cutanea tarda [PCT]); OR
- When the above criteria are not met and for all other indications.

Panhematin (Hemin) is considered experimental/investigational and, therefore, not covered for the following:

- For concurrent use of givosiran with prophylactic panhematin (Hemin) treatment
- When an individual is requesting treatment for other forms of porphyria, such as cutaneous porphyrias (e.g., porphyria cutanea tarda [PCT])
- When the above criteria are not met and for all other indications

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

All requests for givosiran (Givlaari) and panhematin (Hemin) require review by the Company per the policy criteria detailed in this policy bulletin.

If givosiran (Givlaari) or panhematin (Hemin) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

BLACK BOX WARNINGS
Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

BENEFIT APPLICATION

MANDATES
This policy is consistent with applicable state mandates. The laws of the state where the evidence of coverage is issued determine the mandated coverage.

Subject to the terms and conditions of the applicable Evidence of Coverage, givosiran (Givlaari) and panhematin (Hemin) is covered under the medical benefits of the Company’s Medicare Advantage products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met.

However, services that are identified in this policy as experimental/investigational are not eligible for coverage or reimbursement by the Company.

DOSING AND FREQUENCY REQUIREMENTS

For detailed information about Dosing and Frequency Requirements, please see the Policy section.

The Company reserves the right to modify the Dosing and Frequency requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of givosiran (Givlaari) and panhematin (Hemin). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of givosiran

outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for givosiran (Givlaari) or panhematin (Hemin).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Givosiran (Givlaari) was approved by the FDA on November 20, 2019, for the treatment of adult patients with acute hepatic porphyria (AHP).

Panhematin (Hemin) was approved by the FDA on July 20, 1983, for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women.

PEDIATRIC USE

The safety and effectiveness of givosiran (Givlaari) in pediatric individuals have not been established.

The safety and effectiveness of panhematin (Hemin) has been established in pediatric individuals ages 16 and older.

Description

ACUTE HEPATIC PORPHYRIA (AHP)

Acute hepatic porphyria (AHP), caused by gene mutations, has four distinct subtypes. All are caused by missing or deformed genes that produce enzymes involved in the production of heme. Because particles generated in the process of making heme cannot be cleared by individuals who have AHP, toxins that build up in the liver cause unpredictable episodes of pain and other symptoms. Attacks may be associated with triggers, such as certain drugs, smoking or stress, but many have no identifiable cause. Not all individuals have frequent episodes, however, and some cases are milder than others. In the United States, about one person in 25,000 is believed to have some form of porphyria, equaling around 13,000 individuals. Porphyria affects all ethnic groups and all ages. The majority of individuals who have AHP will experience symptoms between the ages of 18 and 45. AHP is more likely to manifest in women than in men; however, symptoms/attacks tend to decrease when women are nearing the age of menopause. Currently, treatments for AHP address only the symptoms/attacks, not the causes of the condition (prophylaxis). They include antihypertensives, pain relievers, and infusions of hemin (an enzyme inhibitor) for acute attacks.

PANHEMATIN (HEMIN)

Panhematin (Hemin; Indivior Manufacturing LLC., Raleigh, NC) is a hemin injection indicated for amelioration of recurrent attacks caused by AHP by rapidly downregulating aminolevulinate synthase 1 (ALAS1) expression in the liver, thus reducing overproduction of aminolevulinic acid (ALA) and porphobilinogen (PBG). Timely initiation of panhematin (Hemin) reduces the accumulation of ALA and PBG leads to an increase and normalization of the rate of heme production. Panhematin (Hemin) can be given to ameliorate symptoms from an acute attack or given prophylactically in individuals with recurrent attacks.

GIVOSIRAN (GIVLAARI)

Givosiran (Givlaari) is an ALAS1-directed small interfering RNA that causes degradation of ALAS1 mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of neurotoxic intermediates ALA and PBG, factors associated with attacks and other disease manifestations of AHP.

Givosiran is indicated for the treatment of adult individuals with AHP, a genetic disorder resulting in the buildup of toxic porphyrin molecules that are formed during the production of heme (which helps bind oxygen in the blood). Individuals who have the condition are missing or have defects in some of the liver enzymes important in eliminating

byproducts of making heme, the iron-rich part of blood that moves oxygen around the body. As a result of the toxins (porphyrins) that accumulate, individuals who have AHP experience sudden attacks that often involve intense pain that may last for several days or weeks, and that can lead to hypertension, neurologic damage, respiratory failure, seizures, and even death.

PEER-REVIEWED LITERATURE

SUMMARY
On November 20, 2019, the US Food and Drug Administration (FDA) approved givosiran (Givlaari) subcutaneous (SC) injection. The FDA also designated givosiran (Givlaari) as an orphan drug, under both Breakthrough Therapy and Priority Review programs. Approval was based on positive results from the study titled ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study With an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients With Acute Hepatic Porphyrias, a randomized, double-blind, placebo-controlled, multinational study of 94 individuals with AHP, at 36 study sites in 18 countries—the largest interventional study conducted on AHP. In ENVISION, individuals with AHP who received givosiran (Givlaari) experienced 70% (95% confidence interval [CI], 60%–80%) fewer porphyria attacks compared to placebo over 6 months. Givosiran (Givlaari) also resulted in a similar reduction in intravenous hemin use, as well as reductions in urinary ALA and PBG. Treated individuals had less need for hemin infusions, emergency room services, and hospitalizations, as well.

In the pivotal ENVISION study, the most common adverse reactions (reported in at least 20% of individuals) with givosiran (Givlaari) were nausea (27%) and injection site reactions (25%). Other adverse reactions seen in individuals treated with givosiran (Givlaari) (occurring >5% more frequently than placebo) include rash, serum creatinine increase, transaminase elevations, and fatigue. There are warnings for anaphylactic reaction, hepatic toxicity, renal toxicity, and injection site reactions.

The recommended dosing for givosiran (Givlaari) is 2.5 mg/kg SC once every month by a healthcare provider. Injections should be administered in a facility that is equipped and staffed to handle any anaphylactic reactions that may occur.

Ventura et al. (2022) performed an interim analysis of an extension of the ENVISION study. The goal was to observe the efficacy and safety of givosiran for AHP over 24 months as part of a 36-month open label extension of ENVISION. Note that the protocol during this part of the study was amended and a lower dose (1.25 mg/kg) was introduced; however, for patients on the lower dose with no clinically relevant transaminase elevations, the dose was increased to 2.5 mg/kg. Those who remained on givosiran (Givlaari) along with a placebo crossover group observed a reduction in median annualized attack rate (AAR) of composite porphyria attack. The givosiran (Givlaari) group had a reduction of AAR from 1.00 during the double-blind portion to 0.00 during the OLE period. The placebo crossover group had a decrease from 10.65 during the double-blind portion to 1.35 in the OLE period. Several other efficacy outcomes along with quality-of-life components and safety outcomes were also examined. The most common adverse reactions in both the placebo crossover and continuous givosiran groups (combined) were injection-site reactions (37%), nausea (34%), fatigue (23%), nasopharyngitis (23%), and headache (20%). Thirty percent of the combined group had serious AE and 29% had any severe AE. The authors conclude that long-term use of givosiran (Givlaari) has an acceptable safety profile and significantly benefits individuals with AHP who suffer from recurrent attacks through the reduction of the frequency of attack, hemin use, while improving the severity of pain and quality of life. This study was limited by the changes to the protocol regarding dosage during the open label extension. It was also observed that several participants had elevated blood homocysteine levels, which the authors identify as requring further examination.

Wang et al. (2022) performed a post-hoc analysis of participants in the phase 3 ENVISION study to better understand their disease burden. Several outcomes were examined including AAR in acute intermittent porphyria (AIP) and AHP, rate of hemin doses, daily worst scores for pain, fatigue, and nausea, along with quality-of-life assessments. There was a linear relationship between time since diagnosis and AAR in the placebo group, which suggested that without treatment, the disease progressively became worse. They highlight that their findings revealed that individuals with low rates of attacks still have a severe disease burden and givosiran (Givlaari) can help manage certain acute and chronic porphyria symptoms. The authors acknowledge that their results should be interpreted carefully as it is a post-hoc analysis and lacks predetermined formal statistical comparators.

Kuter et al. (2023) provided final results for the full 36-month open label extension (OLE) of the ENVISION trial. Seventy-nine of 94 completed the study. Similar to previously reported results, treatment with givosiran (Givlaari) was associated with a decrease in AAR. Individuals in the initial treatment group (i.e., 6-month double blind) had a median AAR of 1.0 and median AAR of 0.4 during the OLE crossover. For individuals in the initial placebo crossover group, the median AAR was 10.7, which decreased to 0.9 during the OLE. Reduced median hemin use was demonstrated in the initial treatment group (0 to 0.4) and after the placebo crossover (16.2 to 0.4). Thirty-seven of 94

participants (39%) experienced a serious adverse event, with the most common event being increased blood homocysteine. The authors note that all efficacy endpoints in the OLE were exploratory and no clinical determinations can be drawn from the additional analysis. Additional study limitations were previously reported in the above Ventura et al. (2022) analysis.

References

Balwani M, Gouya L, Rees DC, 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. April 13, 2019. European Association for the Study of the Liver (EASL) 54th Annual International Liver Congress. Vienna, Austria.

DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed March 4, 2025.

Elsevier's Clinical Pharmacology Compendium. Givosiran (Givlaari). Updated 02/15/2025. [Clinical Pharmacology Web site]. Available at: https://www.clinicalkey.com/pharmacology/ [via subscription only]. Accessed March 4, 2025.

Elsevier's Clinical Pharmacology Compendium. Panhematin (Hemin). Updated 01/11/2024. [Clinical Pharmacology Web site]. Available at: https://www.clinicalkey.com/pharmacology/monograph/2851?aprid=90215 [via subscription only]. Accessed March 4, 2025.

Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol*. 2023;79:1150-1158.

Lexi-Drugs Compendium. Givosiran (Givlaari). Updated 12/15/2024. [Lexicomp Online Web site]. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed March 4, 2025.

Lexi-Drugs Compendium. Panhematin (Hemin). Updated 01/17/2025. [Lexicomp Online Web site]. Available at: https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7021?cesid=4sAlUSkOzyj&searchUrl=/lco/action/search?q=panhematin&t=name&acs=false&acq=panhematin#doa. Accessed March 4, 2025.

Merative Micromedex. Panhematin (Hemin). Updated 06/14/2024. [Micromedex Online Web site]. Available at: https://www.micromedexsolutions.com/micromedex2/librarian/CS/98F9EC/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/2DDBE1/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=274400&contentSetId=100&title=Hemin&servicesTitle=Hemin&brandName=Panhematin&UserMdxSearchTerm=panhematin&=null#quickanspanelprint. Accessed March 4, 2025.

NCT03338816. ENVISION: A study to evaluate the efficacy and safety of givosiran (ALN-AS1) in patients with acute hepatic porphyrias (AHP). ClinicalTrials.gov. U.S. National Library of Medicine. Available at: https://clinicaltrials.gov/ct2/show/NCT03338816?term=nct03338816&draw=1&rank=1. Accessed March 4, 2025.

National Institute for Health and Care Excellence. Givosiran for treating acute hepatic porphyria. Highly specialized technologies guidance. Reference number:HST16. Published: 24 November 2021. Available at: https://www.nice.org.uk/guidance/hst16. Accessed March 4, 2025.

Porphyria. American Porphyria Foundation (APF). 2010-2020. Available at: https://porphyriafoundation.org/for-healthcare-professionals/healthcare-professional-portal/. Accessed March 4, 2025.

Porphyrias Consortium. Rare Diseases Clinical Research Network. National Institutes of Health. Available at: https://pc.rarediseasesnetwork.org/. Accessed March 4, 2025.

Truven Health Analytics Inc. Micromedex DrugDex® Compendium. Givosiran (Givlaari). [Micromedex® Solutions Web site]. Updated 02/10/2025. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [via subscription only]. Accessed March 4, 2025.
May 5, 2024.

Ventura P, Bonkovsky HL, Gouya L, et al. Efficacy and safety of givosiran for acute hepatic porphyria: 24-month interim analysis of the randomized phase 3 ENVISION study. *Liver Int*. 2022;42(1):161-172. doi:10.1111/liv.15090.

Wang B, Ventura P, Takase KI, et al. Disease burden in patients with acute hepatic porphyria: experience from the phase 3 ENVISION study. *Orphanet J Rare Dis*. 2022;17(1):327. doi:10.1186/s13023-022-02463-x.

Wang B, Bonkovsky HL, Lim JK, et al. AGA Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review. *Gastroenterology.* 2023;164(3):484-491.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drugs @FDA. Givosiran (Givlaari) Prescribing Information. Updated 04/2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212194s007lbl.pdf. Accessed March 4, 2025.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drugs @FDA. Panhematin (Hemin) Prescribing Information. Updated 05/2020. Available at: https://www.panhematin.com/wp-content/themes/panhematin/assets/pdf/panhematin-marketing-PI.pdf. Accessed March 4, 2025.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)

J0223 Injection, givosiran, 0.5 mg
J1640 Injection, hemin, 1 mg

Policy History

Revisions From MA08.112a:

09/16/2025	This version of the policy will become effective 09/16/2025. The policy's title has been revised to include panhematin (Hemin). Eligibility criteria have been added to this policy for panhematin (Hemin) therapy.

	The following HCPCS code has been added to this policy: J1640 Injection, hemin, 1 mg The following ICD-10 codes have been removed from this policy: E80.20 Unspecified porphyria E80.21 Acute intermittent (hepatic) porphyria E80.29 Other porphyria

MA08.112:

03/28/2025	The policy has been reviewed and reissued to communicate the Company's continuing position on givosiran (Givlaari®).
05/07/2024	The policy has been reviewed and reissued to communicate the Company's continuing position on givosiran (Givlaari®).
09/05/2023	The policy has been reviewed and reissued to communicate the Company's continuing position on givosiran (Givlaari®).
05/02/2022	This new medical policy has been created to communicate Company's coverage position and criteria forgivosiran (Givlaari®). This medical policy will be effective as of 05/02/2022.

Version Effective Date:
09/16/2025
Version Issued Date:
09/16/2025
Version Reissued Date:
N/A