Givlaari (givosiran) injection, for subcutaneous use

Policy Number: MC/PC 062
Effective Date: June 1, 2026

Instructions for Use

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Related Policies

- n/a

Coverage Rationale

Acute Hepatic Porphyria

For initial coverage of Givlaari (givosiran) injection, for subcutaneous use, for Acute Hepatic Porphyria, the following will be required:

- Patient is 18 years old or greater with a confirmed diagnosis of acute hepatic porphyria (i.e., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, ALA dehydrase deficient porphyria) **and**
- One of the following:
  - Patient has active disease with at least two documented porphyria attacks within the past 6 months
  - Patient is currently receiving treatment with prophylactic hemin to prevent porphyria attacks **and**
- Provider attestation documenting elevated urinary or plasma levels of one of the following within the past 12 months:
  - Porphobilinogen (PBG)
  - Delta-aminolevulinic acid (ALA) **and**
- Patient has not had a liver transplant or be scheduled for a transplant **and**
- Patient will not receive concomitant prophylactic hemin treatment while on Givlaari **and**
- Prescribed by or in consultation with one of the following:
  - Gastroenterologist
  - Hepatologist
  - Hematologist
  - Neurologist
  - A specialist with expertise in the diagnosis and management of acute hepatic porphyria

For reauthorization coverage of Givlaari (givosiran) injection, for subcutaneous use, the following will be required:

- Patient demonstrates positive clinical response while on therapy as demonstrated by one of the following:
  - Reduction in hemin administration requirements
  - Reduction in the rate or number of porphyria attacks **and**
- Patient has not had a liver transplant or be scheduled for a transplant **and**

- Patient will not receive concomitant prophylactic hemin treatment while on Givlaari **and**
- Prescribed by or in consultation with one of the following:
    - Gastroenterologist
    - Hepatologist
    - Hematologist
    - Neurologist
    - A specialist with expertise in the diagnosis and management of acute hepatic porphyria

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0223	Injection, givosiran, 0.5 mg

ICD-10 Code	Description
E80.20	Unspecified porphyria
E80.21	Acute intermittent (hepatic) porphyria
E80.29	Other porphyria

Background

Acute hepatic porphyria (AHP), a subset of porphyria, refers to a family of rare, metabolic diseases characterized by potentially life-threatening acute neurovisceral attacks that involve the autonomic, peripheral, and central nervous systems and typically manifest with severe abdominal pain, tachycardia, hypertension, motor weakness, and psychiatric symptoms (Chan et al 2015, Gouya et al 2019[a]).

Acute attacks may be triggered by several factors, including the use of cytochrome P450 (CYP450)-inducing drugs, dieting, and hormonal fluctuations, all of which may result in the increased expression of hepatic 5-aminolevulinic acid synthase (ALAS1), the first and rate-limiting enzyme of the heme biosynthetic pathway. When ALAS1 activity is induced, the inherited enzyme deficiency becomes limiting and results in the increased hepatic production of the upstream neurotoxic porphyrin precursors, δ-aminolevulinic acid (ALA), and porphobilinogen (PBG), which accumulate in the plasma and urine during attacks. The neurotoxic symptoms that occur with AHP are mainly attributed to the accumulation of ALA and PBG (Chan et al 2015).

There are 4 types of AHPs (Gouya et al 2019[a]):

- Acute intermittent porphyria (AIP) (the most common form of AHP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)
- δ-aminolevulinic acid dehydratase deficiency porphyria (ADP) (the least common of the AHPs)

Givlaari (givosiran) was approved by the U.S. Food and Drug Administration (FDA) in November 2019. It utilizes ribonucleic acid (RNA) interference, a naturally occurring biological process by which small interfering RNAs (siRNA) selectively and robustly silence target messenger RNA (mRNA), effectively suppressing expression/production of the corresponding disease-causing protein (Chan et al 2015).

Clinical Evidence

Clinical Efficacy

The FDA approval of givosiran was based on the ENVISION clinical trial, a 6-month, phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial (N = 94) that evaluated the safety and efficacy of this agent in patients with AHP (AIP, HCP, VP, and ADP). Eligible patients were aged ≥ 12 years, had a confirmed diagnosis of AHP (AIP, HCP, VP, or ADP), elevated urinary or plasma ALA or PBG levels within the prior year, and experienced at least two documented porphyria attacks in the 6 months before enrollment. Key exclusion criteria included clinically significant abnormal laboratory findings, anticipated liver transplantation, a history of multiple drug allergies or intolerance to subcutaneous administration, active HIV, hepatitis B, or hepatitis C infection, and a history of recurrent pancreatitis. Baseline characteristics showed that most patients were female and had genetically confirmed AIP. The mean age was 42 years in the givosiran group and 36 years in the placebo group. Patients experienced a median of four composite attacks in the 6 months preceding randomization. Across treatment groups, approximately 40% had received prior hemin prophylaxis, and about half reported chronic symptoms between attacks (Clinicaltrials.gov Web site, Givlaari PI 2025, Gouya et al 2019[b]).

For the primary endpoint, givosiran reduced the composite mean annualized attack rate (AAR) by 74% compared to placebo ($p < 0.001$; rate ratio [givosiran vs placebo] = 0.26, 95% confidence interval [CI], 0.16 to 0.41). More specifically, the mean composite AAR value in the givosiran group was 3.2 (95% CI, 2.25 to 4.59) vs 12.5 (95% CI, 9.35 to 16.76) in the placebo group. Givosiran also reduced the median composite AAR by 90% compared to placebo (median rate = 1.0 for givosiran and 10.7 for placebo).

The secondary endpoint of annualized days of hemin use demonstrated a statistically significant reduction of 77% for patients in the givosiran group, compared to placebo ($p < 0.001$). ALA and PBG levels also demonstrated statistically significant reductions compared to placebo. Other secondary endpoints, such as daily worst pain, did not demonstrate statistically significant reductions when ANCOVA was used, but did demonstrate a statistically significant reduction when Wilcoxon testing was conducted in a post-hoc analysis ($p < 0.05$).

Clinical Guidelines

The 2023 American Gastroenterological Association (AGA) Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review (Wang et al. 2023) recommends:

- Women aged 15-50 years with unexplained, recurrent severe abdominal pain without a clear etiology after an initial workup should be considered for screening for acute hepatic porphyrias (AHP).
- Initial diagnosis of AHP should be made by biochemical testing measuring δ -aminolevulinic acid, porphobilinogen, and creatinine on a random urine sample.
- Genetic testing should be used to confirm the diagnosis of AHP in patients with positive biochemical testing.
- Acute attacks of AHP that are severe enough to require hospital admission should be treated with intravenous hemin, given daily, preferably into a high-flow central vein.
- In addition to intravenous hemin, management of acute attacks of AHP should include pain control, antiemetics, management of systemic arterial hypertension, tachycardia, hyponatremia and hypomagnesemia, if present.
- Patients should be counseled to avoid identifiable triggers that may precipitate acute attacks, such as alcohol and porphyrinogenic medications.
- Prophylactic heme therapy or givosiran, administered in an outpatient setting, should be considered in patients with recurrent attacks (4 or more per year).
- Liver transplantation for AHP should be limited to patients with intractable symptoms and significantly decreased quality of life who are refractory to pharmacotherapy.
- Patients with AHP should be monitored annually for liver disease.
- Patients with AHP, regardless of the severity of symptoms, should undergo surveillance for hepatocellular carcinoma, beginning at age 50 years, with liver ultrasound every 6 months.

- Patients with AHP on treatment should undergo surveillance for chronic kidney disease annually with serum creatinine and estimated glomerular filtration rate.
- Patients should be counseled on the chronic and long-term complications of AHP, including neuropathy, chronic kidney disease, hypertension, hepatocellular carcinoma and the need for long-term monitoring.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

GIVLAARI (givosiran) is an aminolevulinate synthase 1-directed small interfering RNA indicated for the treatment of adults with acute hepatic porphyria (AHP).

References

1. Chan A, Liebow A, Yasuda M, et al. Preclinical development of a subcutaneous ALASi RNAi therapeutic for the treatment of acute hepatic porphyrias using circulating RNA quantification. *Mol Ther Nucleic Acids*. 2015;4:e263.
2. ClinicalTrials.gov Web site. https://clinicaltrials.gov. Identifier: NCT03338816 – ENVISION (givosiran). Accessed: March 4, 2026.
3. Givlaari [package insert], Cambridge, MA: Alnylam Pharmaceuticals, Inc.; September 2025.
4. 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." *International Congress on Porphyrins and Porphyrias*, 8-11 September 2019 [b], University of Milan, Italy.
5. Gouya L, Ventura P, Balwani M, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology*. 2019[a], 71(5), 1546-1558.
6. Wang B, Bonkovsky HL, Lim JK, et al. AGA Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review. *Gastroenterology* 2023:ISSN: 0016-5085, Vol: 164, Issue: 3, Page: 484-491.

Policy History/Revision Information

Date	Summary of Changes
5/14/2026	Approved by OptumRx P&T Committee

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).