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Policy Number: C17924-A

Givlaari (givosiran)

PRODUCTS AFFECTED

Givlaari (givosiran)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive

DIAGNOSIS:
Acute Hepatic Porphyria (AHP)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. ACUTE HEPATIC PORPHYRIA
1. Documented diagnosis of Acute Hepatic Porphyria [Acute Intermittent Porphyria, Hereditary Corproporphyria, Variegate Porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria] confirmed by genetic testing [DOCUMENTATION REQUIRED]
   AND

2. Active disease documented by at least 2 porphyria attacks* within the last 6 months (*attacks are defined as those that require hospitalizations, urgent healthcare visits, or intravenous hemin administration at home).
   AND
3. Prescriber attests that Member is not *prophylactically* using hemin while on the requested treatment (this does NOT include hemin treatment for acute attacks)
   AND
4. Prescriber attests or reviewer has found no evidence member has ANY of the following (exclusions to therapy): Anticipated liver transplantation, Active HIV, hepatitis C virus, or hepatitis B virus infection(s) or History of recurrent pancreatitis
   AND
5. Prescriber attests that Women of child-bearing potential have a negative serum pregnancy test, agree to use acceptable contraception, and are currently not nursing
   AND
6. Prescriber attests liver function tests have been/will be obtained prior to initiating treatment and repeated every month during the first 6 months of treatment, and as clinically indicated.
   AND
7. Prescriber attests that blood Homocysteine level has been/will be obtained prior to initiating treatment and repeated every month during the first 6 months of treatment, and as clinically indicated thereafter
   AND
8. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Givlaari (givosiran) include: severe hypersensitivity to givosiran, concomitant use with CYP1A2 and CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities]

CONTINUATION OF THERAPY:

A. ACUTE HEPATIC PORPHYRIA

1. Documentation of Prescriber attests to monitoring liver function tests every month during the first 6 months of treatment. Review for elevated transaminase levels which may indicate hepatic toxicity, and as clinically indicated thereafter. AND Homocysteine levels as clinically indicated during treatment.
   AND
2. Documentation of Clinical efficacy confirmed by reduction in frequency of attacks, defined as: reduction from baseline in porphyria attacks that required hospitalizations, urgent healthcare visits or intravenous hemin administration at home. [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests a recent review of member's current medication has been completed and there is no concomitant use of CYP1A2 and CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities (a contraindication)

DURATION OF APPROVAL:

Initial authorization: 6 months; Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified physician specializing in the treatment of porphyria, or specialist at a porphyria treatment center.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually

AGE RESTRICTIONS:

18 years of age or older

QUANTITY:
2.5mg/kg given subcutaneously (SC) once every month

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.
Note: Site of Care Utilization Management Policy applies for Givlaari (givosiran). For information on site of care, see "place holder for hyperlink for Specialty Medication Administration Site of Care coverage criteria policy" Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Hematological Agents

FDA-APPROVED USES:
Indicated for treatment of adults with acute hepatic porphyria (AHP)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Acute Hepatic Porphyria (AHP)

- A group of four inherited diseases of heme biosynthesis that present with episodic, acute neurovisceral symptoms: acute intermittent porphyria (AIP; the most common AHP), variegate porphyria (VP), aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP)
- Each type of AHP results from a genetic defect leading to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver that, when mutated, lead to impaired production of heme, a vital molecule with responsibilities that include oxygen transport in the blood. As a result, particles generated in the process of making heme cannot be cleared by patients who have AHP, toxins that build up in the liver cause unpredictable episodes of pain and other symptoms.
- All 4 variants are characterized by episodic and potentially life-threatening acute neurologic attacks and more likely to manifest in women (80%) than in men and occurs most commonly in women in child-bearing years between 14 and 45 years of age and symptoms/attacks tend to decrease when women near the age of menopause
- Attacks may be associated with triggers, including certain drugs, smoking or stress; but many have no identifiable cause. Not all patients have frequent episodes, however, and some cases are milder than others.
- Diagnosed by finding significantly elevated levels of porphyrin precursors ALA and porphobilinogen in urine/plasma (American Porphyria Foundation, 2019)
- The combined prevalence of these diseases is approximately 5 cases per 100,000 persons (The Porphyrias Consortium, 2019). It is estimated that about 1 in 10,000 Europeans or people of European

ancestry carries a mutation in one of the genes for acute porphyria, although mutations have been found in all races and many other ethnicities.

- Due to the rarity and the nonspecific nature of AHP signs and symptoms, the diagnosis is often missed or delayed as the clinical features resemble other more common medical conditions (i.e. gallstones, appendicitis, inflammatory bowel disease, irritable bowel syndrome, and fibromyalgia)
- Long-term complications and comorbidities of AHP include hypertension, chronic kidney disease or liver disease including hepatocellular carcinoma

Treatment

- The aim of treatment for an acute attack of hepatic porphyria is to abate the attack as quickly as possible and to provide appropriate supportive care and symptomatic care until the acute attack resolves. Hospitalization is usually required.
- Therapy requires confirmation of acute porphyria, based on the finding of elevated urinary porphobilinogen (PBG), either at present or previously. It does not require a diagnosis of the exact type of acute porphyria. In a patient known to have an acute porphyria based on prior testing, the presence of an acute attack is largely established clinically.
- No FDA-approved medications indicated for the *prophylaxis* of porphyria attacks at this time. Current care options generally include trigger avoidance such as certain medications (including porphyrinogenic drugs, hormone drugs, recreation drugs), alcohol uses, dieting or fasting, exposures to sunlight, smoking, emotional or physical stress (including infections and illnesses), menses, and carbohydrate loading.
- There is one FDA-approved treatment option for recurrent attacks: Panhematin (an IV hemin), indicated for the treatment of *acute* attacks and debatable for prophylaxis (not an indication of heme). Blood-derived hemin given IV via central line: Hemin has a short duration of action, requires venous access (often through an indwelling venous catheter), and can have associated side effects (e.g., injection site reactions/phlebitis, coagulopathy, malaise, migraine, memolysis); long-term administration may cause tachyphylaxis or lead to iron overload, venous scarring, and catheter-related infection (Sardh et al., 2019).
- *Orthotopic liver transplantation (OLT)* has been successful and indeed curative in patients with severe, disabling, intractable attacks that are refractory to hemin therapy; however, OLT is associated with morbidity and mortality it is considered a treatment of last resort. (Wang et al., 2018).
- Gene therapy is currently in early stages of research.

Givlaari (givosiran)

- Indicated for the treatment of adults with AHP (FDA approved on November 20, 2019). Administered by a health care professional via subcutaneous injection once monthly at a dose based on actual body weight with medical support available to appropriately manage anaphylactic reactions
- An RNA interference (RNAi) agent that targets the enzyme aminolevulinic acid synthase 1 (ALAS1): First-in-class, small interfering RNA agent that causes degradation of ALAS1 mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA which leads to reduced circulating levels of the neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), porphyrin molecules that contribute to the toxic buildup associated with porphyria attacks and other disease manifestations of AHP
- The best available published evidence includes the ENVISION phase III trial (Balwani et al., 2020*)*. A Phase 1 trial (Sardh et al., 2019) is also published.
- *Pivotal Trial.* FDA-approval was based on positive results of the Phase 3 ENVISION study [*A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients with Acute Hepatic Porphyrias; NCT03338816*] evaluated the safety and effectiveness of givosiran in reducing porphyria attacks in 94 individuals aged ≥ 12 years with AHP. Results found a significant reduction in the rate of acute attacks, defined as attacks requiring a medical visit, hospitalization, or home administration of hemin. Final data showed that patients' annual rate of porphyria attacks decreased by 74% in givosiran-treated patients compared with patients treated with a placebo. Levels of ALA, a key biomarker of AHP, was also reduced in patients' urine by 92%, which was consistent with previous interim data.
- Interim results of the ENVISION Phase 3 study published from the open-label extension period confirm the long-term therapeutic benefit of givosiran in patients with AHP who experience recurrent acute AHP attacks. Results show that the efficacy and safety of givosiran were maintained through 12

months of treatment, with sustained or enhanced reduction in AHP attacks over time. (June 30, 2020) The safety profile was consistent with that observed in the double-blind period of the study, and no new safety findings were reported.

Phase I Trial (Sardh et al., 2019)

A multicenter randomized placebo-controlled trial evaluated the safety, pharmacokinetic, and pharmacodynamic profiles of Givlaari of patients between the ages of 18 and 65 years with a mutation-confirmed diagnosis of acute intermittent porphyria (AIP) and had elevated urinary delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels. A total of 40 patients were enrolled in the study and a total of 23 patients in parts A and B and 17 patients in part C underwent randomization.

The study assessed adverse events (AEs) as well as pharmacodynamic and pharmacokinetic outcomes. Exploratory endpoints were the effect of Givlaari on rates of attacks and hemin use for patients in part C of the study. Attacks were defined as those resulting in hospitalization, urgent care visits, or use of hemin at home.

- In part A of the trial, patients without recent porphyria attacks (i.e., no attacks in the 6 months before baseline) were randomly assigned to receive a single subcutaneous injection of one of five ascending doses of givosiran (0.035, 0.10, 0.35, 1.0, or 2.5 mg per kilogram of body weight) or placebo.
- In part B, patients without recent attacks were randomly assigned to receive once-monthly injections of one of two doses of givosiran (0.35 or 1.0 mg per kilogram) or placebo (total of two injections 28 days apart).
- In part C, patients who had recurrent attacks were randomly assigned to receive injections of one of two doses of givosiran (2.5 or 5.0 mg per kilogram) or placebo once monthly (total of four injections) or once quarterly (total of two injections) during a 12-week period, starting on day 0. Safety, pharmacokinetic, pharmacodynamic, and exploratory efficacy outcomes were evaluated.

Results. Patients with recurrent attacks (part C):

- A single 2.5 mg/kg givosiran dose resulted in rapid, dose-dependent reductions in urinary ALAS1 mRNA level (86%), urinary ALA (91%) and PBG levels (96%)
- Repeat doses of 1 mg/kg 28 days apart caused similar decreases, with levels remaining below baseline at day 70
- 4 monthly doses of 2.5 or 5 mg/kg resulted in ALAS1 mRNA reductions of 67% and 74%, respectively.
- ALA and PBG levels were reduced > 90% from baseline; Annualized attack rate among patients who received givosiran was 7.2, compared to 16.7 in the placebo group and annualized number of hemin doses was 12.1 in the givosiran versus 23.4 in the placebo group
- Association between lower ALA levels and reduced annualized attack rate

Conclusion. Once-monthly injections of givosiran in patients who had recurrent porphyria attacks resulted in mainly low-grade adverse events, reductions in induced ALAS1 mRNA levels, nearly normalized levels of the neurotoxic intermediates delta aminolevulinic acid and porphobilinogen, and a lower attack rate than that observed with placebo. (ClinicalTrials.gov number, NCT02452372).

Pivotal Trial Phase 3 Trial

ENVISION: Efficacy and Safety of Givosiran (ALN-AS1) in Patients with Acute Hepatic Porphyrias (AHP)
FDA approval of Givlaari was based on pivotal ENVISION trial, a Phase 3 randomized, double- blind, placebo-controlled, multinational study of 94 patients with AHP (median age 37.5 years, 89% female), at 36 study sites in 18 countries. This is the largest interventional study conducted in AHP to date.

- Efficacy in the 6-month double-blind period was measured by the rate of porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration at home.
- All patients had ≥ 2 porphyria attacks (requiring hospitalization, urgent healthcare visit, or IV hemin administration at home) in ≤ 6 months before study
- Patients were randomized to receive once monthly injections of either givosiran or placebo for 6 months
- Primary Outcome Measures: Annualized rate of composite porphyria attacks, defined as those attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home, in patients with acute intermittent porphyria (AIP), the most common form of AHP, over six months
    - Secondary outcome measures included the pharmacodynamic (PD) effect of Givlaari on urine

levels of delta-aminolevulinic acid, PD effect of Givlaari on urine levels of PBG, annualized rate of hemin administrations, annualized rate of porphyria attacks in patients with AHP, pain as measured by the Brief Pain Inventory-Short Form numeric rating scale, nausea and fatigue as measured by the Brief Fatigue Inventory-Short Form numeric rating scale, and change from baseline in the Physical Component Summary of the 12-Item Short Form Survey (SF-12).

Results

- Comparing givosiran vs. placebo at 6 months:
  - Mean rate of porphyria attacks 1.9 vs. 6.5 ($p < 0.0001$): The rate of porphyria attacks that required hospitalization, urgent healthcare visit, or IV hemin administration at home was significantly lower with givosiran treatment (mean rate, 1.9; 95% CI, 1.3 to 2.8) compared with placebo (mean rate, 6.5; 95% CI, 4.5 to 9.3).
  - Mean days of hemin use 4.7 vs. 12.8 ($p = 0.0002$): The mean amount of days of hemin use was significantly lower in the givosiran group (mean days, 4.7 (95% CI, 2.8 to 7.9) vs 12.8 (95% CI, 7.6 to 21.4).
  - The rate of porphyria attacks that required hospitalization, urgent healthcare visit, or IV hemin administration at home was significantly lower with givosiran treatment compared with placebo, with 70% of patients receiving givosiran experiencing fewer porphyria attacks, in a randomized trial.
- Patients with AHP taking Givlaari on average experienced 70% fewer porphyria attacks (95% CI: 60%, 80%) compared to those taking placebo.
- Givlaari also resulted in a similar reduction in intravenous hemin use with an average reduction of 77% in the number of annualized days taking hemin, as well as reductions in urinary ALA and PBG, with mean reductions of 91% and 83% in urinary ALA at three months and six months, respectively.
- Results also showed that the 46 Givlaari-treated patients were on track for an expected average of 3.2 porphyria attacks per year after 6 months, versus an anticipated average of 12.5 attacks per year for the 43 patients in the placebo arm.
- The manufacturer also reported that 50% of Givlaari-treated patients were attack-free during the six-month treatment period as compared to 16.3% for those in the placebo arm.

Adverse events

- Injection site reactions were reported in 25% of patients receiving Givlaari in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site.
- The most common AEs in the Givlaari groups were nasopharyngitis (27%), abdominal pain (24%), nausea (18%), and diarrhea (12%). Seven serious AEs in 6 patients were reported in the Givlaari groups. One patient receiving Givlaari died from hemorrhagic pancreatitis; however, it was determined that this incident was unlikely related to the study drug. Other adverse reactions seen in patients treated with Givlaari (givosiran) (occurring over 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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Givlaari (givosiran) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications include hypersensitivity to givosiran or any component of the formulation and concomitant use with CYP1A2 or CYP2D6 substrates. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

OTHER SPECIAL CONSIDERATIONS:

Dosing of Givlaari (givosiran) is based on actual body weight.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0223	Injection, givosiran, 0.5 mg

AVAILABLE DOSAGE FORMS:
Givlaari SOLN 189MG/ML

REFERENCES

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15. Balwani M, Wang B, Anderson KE, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. *Hepatology*. 2017;66(4):1314–1322. doi:10.1002/hep.29313. Available at: Link Accessed December 2020.

SUMMARY OF REVIEW/REVISIONS	DATE

REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Age Restrictions Other Special Considerations References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file