Subject: Givlaari (givosiran)	**Original Effective Date:** Q1 2020
Policy Number: MCP-356	**Revision Date(s):**
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Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Givlaari (givosiran)** for the treatment of adult patients with acute hepatic porphyria, a genetic disorder resulting in the buildup of toxic porphyrin molecules which are formed during the production of heme when appropriate criteria are met.

The intent of this policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

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

CLINICAL EVIDENCE

- 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.

FDA INDICATIONS

Acute Hepatic Porphyria Treatment of adults with acute hepatic porphyria (AHP)

- *The FDA approved a new drug application (NDA) for Givlaari for the treatment of adults with AHP and granted Givlaari orphan drug status and breakthrough therapy designation.*

Available as: 189 mg/mL in a single-dose vial

FDA Approved: November 20, 2019
Black Box Warnings/REM: None at the time of this writing

Pharmacologic Category: Hematological Agents; RNA interference (RNAi) therapy; Aminolevulinate Synthase 1-Directed Small Interfering Ribonucleic Acid (siRNA)

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Givlaari (givosiran) for the treatment of adult patients with **Acute Hepatic Porphyria (AHP)** may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Prescriber specialty [ONE]

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

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

Informational: Additional physicians can be found through the American Porphyria Foundation (APF) or the Porphyria Centers of Excellence such as the Porphyrias Consortium which includes five of the leading porphyria centers in the U.S. that provide expertise and experience in the diagnosis and treatment of porphyria.

2. Diagnosis/Indication [ALL]

Documentation of ALL the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis

❒ Diagnosis of Acute Hepatic Porphyria [Acute Intermittent Porphyria, Hereditary Corproporhyria, Variegate Porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria] confirmed by genetic or biochemical testing
- *Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination (Balwani, 2017)*

❒ Biochemical testing. Markedly elevated levels of the following tests within the past year: [BOTH]
- ❍ Urinary or plasma porphobilinogen (PBG)

AND

- ❍ Urinary delta-aminolevulinic acid (ALA) OR total urine porphyrins

Informational
- *The gold standard in diagnosing AHP in individuals without disease symptoms is measuring the blood and urine levels of ALA and PBG, key factors in heme production.*
- *If urine ALA and PBG are normal during an attack, it essentially rules out an acute porphyria. If urine ALA and PBG are markedly increased, a diagnosis of an acute porphyria is confirmed and further testing is needed to identify the type of acute porphyria. In some patients with acute porphyria, urinary porphyrins may remain increased longer than ALA and PBG. However, mild increases in urinary porphyrins can occur in other medical conditions and is therefore much less specific than increases in ALA and PBG.*

- ❒ 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).

- ❒ Member is not *prophylactically* using hemin while on the requested treatment (this does NOT include hemin treatment for acute attacks)

3. Age/Gender/Restrictions [ALL]

- ❒ 12 years of age or older

- ❒ Women of child-bearing potential: [ALL]
  - ❍ Negative serum pregnancy test; and
  - ❍ Agrees to use acceptable contraception; and
  - ❍ Currently not nursing

- ❒ Member does not meet ANY of the following (exclusions to therapy): [ANY]
  - ❍ Anticipated liver transplantation
  - ❍ Active HIV, hepatitis C virus, or hepatitis B virus infection(s)
  - ❍ History of recurrent pancreatitis

**The use of Givlaari was not studied in the above patient population.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Precipitating factors for attacks/symptoms have been considered and avoided if possible, including porphyrinogenic drugs with safe alternatives. Documentation required.

  NOTE: *Drugs are one of the most significant precipitating factors of attacks in the acute porphyrias, which may be potentially fatal. It is essential to identify those drugs that may provoke an acute attack, and avoid prescribing them, except where no safer alternative exists and the indication outweighs the risks. Drug Database for Acute Porphyria are available at*: http://www.porphyriafoundation.com/drug-database, http://www.drugs-porphyria.org/

- ❒ Liver function tests performed prior to initiating treatment (submission required with initial request) and repeated every month during the first 6 months of treatment, and as clinically indicated thereafter. Documentation required.
  - *Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients receiving Givlaari (givosiran) in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.*

5. Contraindications*/Exclusions/Discontinuations

** Givosiran carries no black box warnings or contraindications*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity (e.g., anaphylaxis) to givosiran or any component of the formulation
- ❒ 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.

Exclusions

- ❒ Pregnancy
- ❒ Anticipated liver transplantation
- ❒ Active HIV, hepatitis C virus, or hepatitis B virus infection(s)
- ❒ History of recurrent pancreatitis

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: *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.*

REAUTHORIZATION /CONTINUATION OF THERAPY

Continuation of therapy with Givlaari (givosiran) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. **Initial Coverage Criteria**
   - ❑ Member currently meets ALL initial coverage criteria

2. **Adherence to Therapy/Compliance**
   - ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's claims history (review Rx history for compliance)
     NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy
   - ❑ Liver function tests: Compliance to recommended liver function tests testing every month during the first 6 months of treatment. Review for elevated transaminase levels which may indicate hepatic toxicity, and as clinically indicated thereafter. Documentation required.
   - ❒ Dose Modification for Adverse Reactions (if applicable): Prescriber submit documentation and/or treatment plan addressing transaminase elevations
     Recommendation: Interrupt or discontinue treatment with Givlaari (givosiran) for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

3. **Labs/Reports/Documentation required [ALL]**
   - ❑ Clinical efficacy confirmed by significant reduction in frequency of attacks, defined as: ≥ 70% reduction from baseline, in fewer porphyria attacks that required hospitalizations, urgent healthcare visits or intravenous hemin administration at home. Documentation required.

4. **Discontinuation of Treatment**
   - ❑ Intolerable adverse effects or drug toxicity
   - ❑ Contraindications/Exclusions to therapy [ANY]

     Authorization will not be granted if ANY of the following conditions apply [ANY]
     - ❍ Non-FDA approved indications
     - ❍ Hypersensitivity (e.g., anaphylaxis) to givosiran or any component of the formulation
     - ❍ 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.

     Exclusions
     - ❍ Pregnancy
     - ❍ Anticipated liver transplantation
     - ❍ Active HIV, hepatitis C virus, or hepatitis B virus infection(s)
     - ❍ History of recurrent pancreatitis

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- ❒ 2.5mg/kg given subcutaneously (SC) once every month by a healthcare provider in a facility that is equipped and staffed to handle any anaphylactic reactions that may occur.
  - *As per the FDA labeled package insert dosing section: Dosing is based on actual body weight.*
  - *Missed dose: Administer Givlaari (givosiran) as soon as possible after a missed dose. Resume dosing at monthly intervals following administration of the missed dose.*

2. Authorization Limit [ALL]

- ❒ Quantity limit: 2.5mg/kg given subcutaneously (SC) once every month

- ❒ Duration of therapy
  - ❍ May authorize up to 3 months of initial therapy
  - ❍ Continuation of therapy may be authorized for up to one year. Subsequent approval will be based on continuous progress notes from the Prescriber documenting improvement from baseline.

3. Route of Administration [ALL]

- ❒ Administered by a health care professional in a facility with medical support available to appropriately manage anaphylactic reactions

- ❒ Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

Coverage Exclusions

This policy addresses the coverage of **Givlaari (givosiran)** for the treatment of adult patients with acute hepatic porphyria, a genetic disorder resulting in the buildup of toxic porphyrin molecules which are formed during the production of heme when appropriate criteria are met.

All other uses of Givlaari (givosiran) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

Background/Clinical Evidence

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 givosarin 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 givosarin 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 givosarin 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.

CLINICAL PRACTICE GUIDELINES

No guidelines were identified that recommend the use of Givlaari for the prevention of acute attacks in AHP.

DEFINITIONS

Acute intermittent porphyria (AIP): an acute type of hepatic porphyria resulting from a deficiency of the enzyme, hydroxymethylbilane synthase (HMB-synthase)

Aminolevulinic acid dehydratase deficiency porphyria (ALAD): an acute type of hepatic porphyria resulting from a deficiency of the enzyme, ALA-dehydratase

Hereditary Coproporphyria (HCP): an acute porphyria due to a deficient activity of the enzyme, coproporphyrinogen oxidase

Variegate Porphyria (VP): an acute type of porphyria due to a deficiency of protoporphyrinogen oxidase. Variegate porphyria has symptoms similar to those of AIP but also to those of a classic photosensitive skin disorder.

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND 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.

CPT	Description

HCPCS	Description
C9056	Injection, givosiran, 0.5 mg
HCPCS C-Codes effective April 1, 2020	

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

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Policy History	Approval
Policy Developed Peer Review: AMR Peer Review Network. 1/4/2020. Practicing Physician. Board certified in Gastroenterology	P&T Q1 2020
Annual Review* No coverage criteria changes with this annual review Content update: • Added published interim data: 12-Month Interim Data from the ENVISION Phase 3 Study of Givosiran in Acute Hepatic Porphyria	Q1 2021

**Annual Review and Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.*