Molina Clinical Policy
Scenesse (afamelanotide) Implant: MEDICARE
Policy No. 367b

Last Approval: 04/10/2024
Next Review Due By: April 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. 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 (e.g., 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 the Federal government or CMS for Medicare. 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 and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Erythropoietic Protoporphyria (EPP) and **X-linked protoporphyria (XLPP)** are inherited cutaneous porphyrias characterized clinically by acute non-blistering photosensitivity, intolerance to sunlight, and a significantly reduced quality of life (QOL). EPP is characterized by a deficiency of the ferrochelatase (FECH) enzyme in the heme biosynthetic pathway, resulting in the accumulation of protoporphyrin IX (PPIX), a light-sensitive molecule, in erythrocytes. A FECH enzyme deficiency causes severe, painful cutaneous photosensitivity and incapacitating burning sensations in the skin during or after exposure to sunlight, especially outdoors, even with some forms of artificial light and an overcast sky (Balwani 2017; Balwani 2019; Langendonk 2015). In XLPP, the genetic defect is a gain-of-function mutation, usually a four-base deletion, in the gene that encodes the enzyme 5-aminolevulinic acid synthase-2, the first and rate-controlling enzyme of heme synthesis in developing red blood cells. An excessive amount of PP can culminate in severe photosensitivity, which can be triggered by any wavelength of light from ultraviolet to blue. Burning, tingling, and itching occur within 30 minutes of sun exposure, followed by erythema and swelling. Symptoms may persist for hours or days after the initial phototoxic reaction, appearing out of proportion to the visible skin lesions. Burning, itching, and excruciating pain may occur without evident skin damage, and blisters or bullae are often absent or infrequent (Balwani 2017). EPP may potentially cause complications with the liver and gallbladder. An estimated 20%-30% of EPP patients have some degree of liver dysfunction (i.e., mild with minor elevations in liver enzymes), and up to 5% may develop more advanced liver disease, which may be accompanied by motor neuropathy like that seen in acute porphyrias. In rare instances, affected individuals may also develop liver disease, leading to liver failure and the need for a transplant. The diagnosis is based on symptoms and increased levels of protoporphyrin in red blood cells and plasma. The diagnostic gold standard for EPP is biochemical analysis interpreted in the context of clinical characteristics. The condition typically manifests in infancy or early childhood after sun exposure with acute, painful photosensitivity; however, in some cases, onset may not occur until adolescence or adulthood. It is the third most frequent porphyria in children, with an estimated prevalence of 1 in 74,300 persons, with both genders equally affected (American Porphyria Foundation).

There are few effective treatment options for treating EPP. Cutaneous symptom management has primarily focused on strict light avoidance (e.g., the use of sun protective clothing, window tinting or films for the vehicle or house) (Balwani 2017). The long-term effects of light avoidance on physical and psychological wellbeing are unknown, but it has been linked to anxiety, social isolation, and poor QOL. Other EPP treatments are symptomatic and supportive. Sunscreens containing physical reflecting agents (e.g., zinc oxide, titanium dioxide) or tanning creams that increase skin pigmentation (e.g., creams containing dihydroxyacetone) may help to some patients. Oral beta-carotene, a high potency form of oral beta-carotene, has been used to improve affected sunlight tolerance, but there is no evidence to support this treatment. Vitamin D supplements are recommended because EPP patients are likely to have low vitamin D levels due to avoiding sunlight. Patients with liver failure may require liver transplantation; however, liver transplantation is not curative because the bone marrow is the primary source of excess protoporphyrin production.

Scenesse (afamelanotide) is indicated to increase pain-free exposure to light in adult patients with a history of phototoxic reactions to EPP. There were no FDA-approved treatments for EPP to increase light exposure prior to the approval of Scenesse. Afamelanotide is a symptomatic treatment for EPP, PPIX levels remain the same and it

is unlikely to protect against PPIX-mediated liver damage; however, therapy may provide an improvement in increasing light exposure. Afamelanotide, a synthetic analog of α-melanocyte stimulating hormone, mimics the naturally occurring hormone by increasing melanin production in melanocytes, resulting in improved sunlight tolerance in EPP/XLPP patients. Afamelanotide is a melanocortin-1 receptor agonist that causes melanocytes to produce eumelanin, which pigments the epidermis and thus protects against light-induced phototoxicity. One implant is administered every 2 months prior to expected and during increased sunlight exposure (e.g., from spring to early autumn). Two Phase 3 studies in the United States and European Union demonstrated the efficacy and safety of Scenesse (Study CUV039, NCT 01605136, and Study CUV029, NCT 00979745).

COVERAGE POLICY

Scenesse (afamelanotide) for the treatment of EPP **may be considered medically necessary** when **ALL** the following clinical criteria are met:

1. Definitive diagnosis of EPP or X-linked protoporphyria (known as XLP or XLEPP) confirmed by genetic testing **AND** Gene sequencing shows a FECH, CLPX, or ALAS2 mutation.

2. Biochemical finding of a marked increase of EPP (e.g., elevated free protoporphyrin in peripheral erythrocytes) confirmed by **ONE** of the following tests:
    a. Elevated total erythrocyte protoporphyrin (e.g., 300 to 8,000 mcg/dL)
    **Normal ranges up to 80 mcg/dL*
    b. Elevated Erythrocyte fractionation shows ≥ 50% metal-free vs. zinc protoporphyrin
    **Generally, metal-free protoporphyrin represents > 85% of total porphyrin in EPP and 50-85% of total porphyrins in XLP*

3. Evidence of EPP/XLP-associated acute non-blistering cutaneous reactions (e.g., pain, stinging, redness, swelling, blanching) following exposure to sun.

4. Documentation of **ALL** the following required.
May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information:
    a. Sun avoidance and use of sunscreen, protective clothing, and pain medication have proven inadequate in controlling EPP-associated painful skin reactions.
    b. Member will continue to maintain sun and light protection measures during treatment to prevent phototoxic reactions.
    c. Member does not have any malignant or premalignant skin lesions (e.g., melanoma, dysplastic nevus syndrome, Bowen's disease, basal cell, or squamous cell carcinomas, etc.) as evidenced by a baseline full body skin examination for pre-existing skin lesions.

5. Prescriber agrees to submit documentation of full-body skin examination twice annually to monitor pre-existing and new skin pigmentary lesions.

    NOTE: Subsequent authorizations require full skin examination. Clinical documentation must be submitted for initial request and for continuation of treatment requests.

CONTINUATION OF THERAPY

Member meets **ALL** the following criteria for re-treatment. Clinical documentation required.

1. Member has met initial criteria for Scenesse therapy.

2. Scenesse therapy may be re-authorized when stabilization of disease, or absence of disease progression is documented by at least **ONE** of the following:
    a. Decreased severity and number of phototoxic reactions.
    b. An increase in pain-free time during light exposure.
    c. Improvement in acute non-blistering cutaneous reactions (e.g., pain, stinging, redness, swelling, blanching) following exposure to sun.

d. Improvement on a pain-intensity Likert scale or QOL questionnaire.

3. Continuous adherence to therapy as verified by member's claim history (review member's prescription claims history for compliance). Any indicator of compliance or adherence issues should be discussed with discussed among treating physician, Member, and Medical Director for a treatment plan or discontinuation of treatment.

4. Member has received a full skin examination by the Prescriber/Dermatologist within the last six months to monitor pre-existing and new skin pigmentary lesions.
NOTE: Clinical documentation must be submitted with every continuation of treatment request.

5. Member has not experienced unacceptable toxicity, significant non-anaphylactic reaction(s), or anaphylaxis from Scenesse Implant therapy.

LIMITATIONS AND EXCLUSIONS

The following are considered **contraindications/exclusions** based on insufficient evidence:

1. Hypersensitivity to Scenesse or its inactive ingredient (e.g., poly [DL-lactide-co-glycolide] bioresorbable copolymer).
2. Any of the following ONE of the conditions:
   a. EPP with significant hepatic involvement.
   Hepatic dysfunction may occur in 20-30% of patients with EPP. Pivotal trials do not include patients clinically significant hepatic or another organ dysfunction.
   b. Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions.
   c. Any other photodermatosis such as polymorphic light eruption, actinic prurigo, discoid lupus erythematosus, chronic actinic dermatitis or solar urticaria.

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above.

PRESCRIBER REQUIREMENTS: Prescribed and administered by a dermatologist or a specialist with expertise in the diagnosis and management of EPP.

AGE RESTRICTIONS: 18 years of age or older.
The safety and effectiveness have not been established in pediatric patients.

DOSING CONSIDERATIONS: The recommended dose is a single implant (16 mg) inserted every 2 months by a health care professional.

MONITORING PARAMETERS: Full body skin examination (twice yearly) per approved labeling.

DURATION OF APPROVAL

1. Initial authorization: **6 months.**
2. Continuation of treatment: Re-authorization is required every **6 months** to determine continued need based on member meeting 'Continuation of Therapy' criteria.

QUANTITY LIMITATIONS

1. ONE implant every 2 months.
2. THREE implants per year for seasonal coverage (most likely during spring and summer) is recommended. The recommended maximum number of implants is FOUR per year.
EXCEPTIONS: For requests beyond THREE implants a year: Medical justification is required; Prescriber submit all relevant supporting documentation for clinical staff review.

ADMINISTRATION

1. Administration by a health care professional who is proficient in the subcutaneous implantation procedure and

has completed the training program provided by the manufacturer (Clinuvel)
Informational Note: The afamelanotide implant should be inserted using an SFM Implantation Cannula or other implantation devices that have been determined by the manufacturer to be suitable for implantation of Scenesse. Refer to the Prescribing Information for specific implantation instructions. Contact Clinuvel Inc. for other implantation devices that have been determined by the manufacturer to be suitable for implantation of Scenesse.

2. Refer to MHI Policy & Procedure *Specialty Medication Administration Site of Care Policy: MHI Pharm 11.*
NOTE: Authorization is generally for administration in physician office setting only. Routine administration in a hospital or outpatient setting will not be authorized.

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.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: Subcutaneous Implantation

DRUG CLASS: Alpha-Melanocyte Stimulating Hormone Analog, Synthetic

FDA-APPROVED USES: Erythropoietic Protoporphyria (EPP)
To increase pain free light exposure in adult patients with a history of phototoxic reactions from EPP

COMPENDIAL APPROVED OFF-LABELED USES: None

SUMMARY OF MEDICAL EVIDENCE

Langendonk et al. (2015) evaluated the safety and efficacy of afamelanotide in treating photosensitivity in patients with EPP in two Phase 3 multicenter, randomized, double-blind, placebo-controlled trials. The two parallel group clinical trials were conducted in the European Union (EU) (n=74) and the United States (US) (n=94) and served as the basis for FDA approval. Adults with EPP were randomly assigned to receive either Scenesse 16 mg or a placebo form of the implant subcutaneously every 60 days. Participants in the US trial received three implants over the course of six months, while those in the EU trial received five implants over the course of nine months. Both trials measured the number of hours a patient could be exposed to direct sunlight without experiencing pain. The primary efficacy endpoint was the duration of pain-free direct exposure to sunlight (10 am to 3 pm in the EU trial vs. 10 am to 6 pm in the US trial). In the U.S. trial, sunlight tolerance was assessed for a greater number of hours per day, and most of the study period occurred during the summer months. The primary outcome in the US trial was in direct sunlight, whereas the primary outcome in the EU trial was in direct sunlight and shade During the study period, the type and duration of sun exposure, the number and severity of phototoxic reactions, and adverse events (AEs) were all recorded. The number of study drug doses administered (3 doses vs. 5 doses), trial duration (6 months vs. 9 months), and time windows within a day in which time spent outdoors was recorded (10 am to 3 pm in the EU trial and 10 am to 6 pm in the US trial) differed between trials.

Source	Trial	Location, Duration, # Enrolled	Primary Outcome(s)
Langendonk 2015 (NCT00979745)	CUV029	European Trial 9 months (5 doses) 5 implants then followed for 270 days N=74 [Scenesse 16mg (n=38); placebo (n=36)]	Time (hours) in light with no pain between 10:00 to 15:00/person/study period

Langendonk 2015 (NCT01605136)	CUV039	United States Trial 6 months (3 doses) 3 implants then followed for 180 days N=94 [Scenesse 16mg (n=48); placebo (n=45)]	Time (hours) in light with no pain between 10:00 and 18:00/person/study period

Participants were mostly Caucasian (98%), the mean age was 40 years (range 18 to 74 years), and 53% of subjects were male and 47% were female. Pain was rated on an 11-point Likert pain-intensity scale (with scores ranging from 0 to 10; higher scores indicating greater severity of symptoms).

- EU trial: Five implants were administered to 74 patients (N = 74) over 9 months; 38 (n = 38) received afamelanotide, and 36 participants (n = 36) received a placebo. After 9 months, the median duration of pain-free time was 6 hours with afamelanotide and 0.8 hours with placebo. The total number of phototoxic reactions after 9 months was significantly lower with afamelanotide in study 2 (77 vs. 146 reactions). This analysis did not include sun exposure on days when subjects reported spending time in both direct sunlight and shade.

- U.S. trial: Three implants were administered to 93 subjects (N = 93) over 6 months; 48 (n = 48) received afamelanotide and 45 (n = 45) received a placebo subcutaneously every 2 months. The median total number of hours spent in direct sunlight between 10 a.m. and 6 p.m. on pain-free days was 69.4 hours for the Scenesse group versus 41 hours for the placebo group over 180 days. After 6 months, patients who received afamelanotide had 70% more pain-free time in direct sunlight than those who received placebo (median: 69.4 hours vs 40.8 hours).

Both trials showed significant improvement in the primary endpoint with no significant AEs. Scenesse was superior to a placebo in increasing the amount of time patients spent directly exposed to sunlight without experiencing pain. Photosensitivity and improvements in sunlight tolerance were observed in the treatment groups when compared to the placebo group. The duration of pain-free time was longer in the afamelanotide group in both trials: a median duration of 69.4 hours vs. 40.8 hours in the placebo group in the US trial over a 6-month period, and a median duration of 6.0 hours vs. 0.75 hours in the EU trial over a 9-month period. The number of phototoxic reactions was also lower in the afamelanotide group (77 vs. 146) in the EU study. Limitations included the subjectivity of patients' pain assessments, the partial unblinding of patients due to increased skin pigmentation in patients who received Scenesse, and sun avoidance due to fear of painful reactions in patients in both groups who did not develop increased pigmentation. Overall, afamelanotide was associated with increased duration of sun exposure without pain, less severe phototoxic reactions, faster phototoxic reaction recovery time, and enhanced QOL.

Afamelanotide was generally well tolerated in clinical trials. The majority of AEs were mild to moderate in severity, with headache, nausea, nasopharyngitis, and back pain being the most common.

Post-marketing requirements by the FDA indicate a thorough QT clinical study to adequately characterize the effect of afamelanotide on cardiac repolarization. A prospective, longitudinal, registry based observational cohort study assessing long-term safety related to primary AEs, skin cancer and implant-site reactions. Secondary AEs of interest include changes in pigmentary expressions, pregnancy outcomes, effects on lactation and breastfeeding infants, and implantation device malfunction or failure (Beitz JG; NDA approval letter).

National and Specialty Organizations. There are no current treatment guidelines for the management of EPP.

NICE (2023) does not recommend afamelanotide for prevention of phototoxicity in adults with EPP.

SUPPLEMENTAL INFORMATION

Porphyria diseases are a group of metabolic disorders characterized by the excessive accumulation and excretion of porphyrins and their precursors caused by abnormal functioning of heme biosynthesis enzymes. Porphyrias are defined by abnormally high levels of porphyrins in the body caused by deficiencies of certain enzymes required for hemoglobin synthesis. There are at least eight types of porphyria, and symptoms vary depending upon the specific enzyme that is deficient. Individuals who have one type of porphyria are unlikely to develop the others (NORD 2021).

CODING & BILLING INFORMATION

HCPCS (Healthcare Common Procedure Coding System) Code

Code	Description
J7352	Afamelanotide implant, 1 mg

AVAILABLE DOSAGE FORMS: Subcutaneous implant containing 16 mg of afamelanotide.
Implant is a bioresorbable sterile rod measuring approximately 1.7 cm in length and 1.45 mm in diameter. Supplied in a sealed glass vial packaged individually in a cardboard box; not supplied with an implantation device.

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

04/10/2024 Policy reviewed, No changes to coverage criteria. Updated Summary of Medical Evidence and References.
04/13/2023 Policy reviewed and updated. No changes in coverage criteria. Updated references section.
04/13/2022 Policy reviewed and updated. No changes in coverage criteria. Updated references section.
04/05/2021 Policy reviewed and updated. No changes in coverage criteria. Updated references. Clarifications in verbiage include:
- Updated prescriber specialty criterion from: Prescribed and administered by a dermatologist or a specialist *in the treatment of porphyria who has completed training for Scenesse administration*, TO: Prescribed and administered by a dermatologist or a specialist *with expertise in the diagnosis and management of EPP*.
- Removal of '*Prescriber must agree that the member will be monitored by a health care provider for at least 30 minutes after the implant administration*' since this is addressed by the criterion in the administration section ('Administration by a health care professional who is proficient in the subcutaneous implantation procedure and has completed the training program provided by the manufacturer)

Q2 2020 P&T New policy. IRO Specialist Peer Review: 4/12/2020. Practicing Physician. Board certified in Dermatology.

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