BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 07/15/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE:**
	CURRENT EFFECTIVE DATE: 07/15/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

SCENESSE® (afamelanotide)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Scenesse (afamelanotide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is physician specializing in the patient's diagnosis or is in consultation with a Dermatologist

  2. Individual is 18 years of age or older

  3. Individual has confirmed diagnosis of phototoxic reactions from erythropoietic protoporphyria (EPP) confirmed by **BOTH** of the following:

     - Increased total erythrocyte protoporphyrin with metal-free erythrocyte protoporphyrin fraction greater than 3 times the upper limit of normal (ULN) in the range of 300 to 8000 mcg/dL (normal lab value less than 80 mcg/dL) with metal-free erythrocyte protoporphyrin documented as the majority of total erythrocyte protoporphyrin
     - Documented history of phototoxicity associated with EPP (swelling, burning, itching, or redness of the skin during or after sun exposure leading to mild to severe burning pain on sun-exposed areas of the skin)

  4. Individual has undergone baseline full body skin evaluation

  5. Scenesse (afamelanotide) to be administered by a health care professional who has completed the training program provided by the manufacturer prior to administering Scenesse implantation.

  Initial approval duration: 6 months
  The recommended dose of Scenesse is a single Scenesse implant inserted subcutaneously above the anterior supra-iliac crest every 2 months.

- **Criteria for continuation of coverage (renewal request):** Scenesse (afamelanotide) considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Dermatologist

  2. Individual condition has responded while on therapy with response defined as **ONE** of the following:

     - Increase in duration of direct sunlight exposure where no pain was experienced
     - Reduction in severity **OR** number of phototoxic reactions

SCENESSE® (afamelanotide)

3. Individual has been adherent with medication

4. Individual has documentation of full body skin evaluation every 6 months

5. Individual and has not developed any contraindications or other significant adverse drug effects that may exclude continued use, including hypersensitivity (e.g., anaphylaxis)

Renewal duration: 12 months
The recommended dose of Scenesse is a single Scenesse implant inserted subcutaneously above the anterior supra-iliac crest every 2 months.

- Scenesse (afamelanotide) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications included, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

SCENESSE® is indicated to increase pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria (EPP). It is a synthetic analogue of alpha-melanocyte stimulating hormone that increases melanin production and reduces free radical formation and cytokine production. Afamelanotide manages phototoxicity associated with EPP by decreasing skin sensitivity via protective properties of melanin as well as working as an antioxidant targeting reactive oxygen species produced by excited protoporphyrin. It is a controlled released 16mg subcutaneous implant administered once every two months.

Scenesse has been shown to be efficacious in improving sunlight tolerance in patients in two multi-center randomized double blind, placebo-controlled trials, one in Europe and one in the United States. In the U.S. trial, patients receiving afamelanotide had a longer duration of pain-free time of 69.4 hours compared to 40.8 hours in the placebo group. In the European trial, patients receiving afamelanotide had a longer duration of pain-free time of 6 hours compared to 0.8 hours in the placebo group. Time

differences in the two studies was attributed to the geographical difference in location of the study centers in relation to how much sun exposure was available.

EPP or X-Linked protoporphyria (XLP) are both forms of protoporphyria resulting from excess protoporphyrin accumulating initially in bone marrow and ultimately in erythrocytes and plasma. Protoporphyrin are hydrophobic and are deposited in lipid layers of cell membranes – most notably in the endothelial cells of the dermis layer. Sunlight exposure causes protoporphyrin to enter an excited state in which they transfer energy into dissolved oxygen allowing it to form superoxide ions (O_2^-) and hydroxyl ions (OH^-). These highly reactive oxygen species interact with other biological molecules causing tissue damage via lipid peroxidation, oxidation of nucleic acids and polypeptides, complement activation, mast cell degradation, and damage to other biological pathways resulting in cutaneous porphyria manifesting as painful, non-blistering photosensitivity.

Excess protoporphyrin is a result of genetic mutation primarily in genes encoding for FECH and ALAS2, however there has been one report CLPX mutation responsible for the disease.

- Ferrochelatase or FECH is responsible for the final step of heme biosynthesis by inserting the Iron into the protoporphyrin IX ring. In normal conditions, FECH inserts Zinc into the small excess of protoporphyrin left over. Mutations to FECH is considered a loss-of-function which reduces FECH function by ~30% of normal.
- Delta-aminolevulinic acid synthase or ALAS is the initial enzyme of the heme biosynthetic pathway; ALAS2 is a variant responsible for XLP and causes C-terminal deletions resulting in gain-of-function mutations that ultimately lead to excessive production of protoporphyrin. Gene mutation for ALAS2 follows a X-Linked inheritance pattern, thus patients with this mutation are considered to have X-Linked protoporphyria or X-Linked erythropoietic protoporphyria. Patients with XLP have normal FECH function, thus having increased Zinc-liganded protoporphyrin compared to their FECH-EPP counterparts.

Other complications and manifestations of EPP/XLP include, but not limited to:

- Iron deficiency: Iron absorption or distribution may be affected by downregulating effects caused by excessive protoporphyrin.
- Cholestatic liver disease: Rare and occurs in less than 5% of patients. Results from accumulation of protoporphyrin that damage hepatocytes and cholangiocytes causing decrease in biliary excretion of protoporphyrin that will progressively accumulate in the liver, erythrocytes, and plasma.
- Cholelithiasis and cholecystitis: Protoporphyrin are insoluble in water and thus excreted in the bile. Patients with EPP have an increased risk of developing gallstones as well as reduced bile flow due to the excess production or porphyrins.
- Vitamin D deficiency: Primary caused by sun-avoidance.

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	05/16/24	Approved guideline
Clinical Pharmacist	05/06/24	Development

SCENESSE® (afamelanotide)

Coding:

HCPCS: J7352

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Resources:

Literature reviewed 05/16/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Dickey AK, et al. Porphyrias Consortium of the Rare Diseases Clinical Research Network. Evidence-based consensus guidelines for the diagnosis and management of erythropoietic protoporphyria and X-linked protoporphyria. *J Am Acad Dermatol*. 2023 Dec;89(6):1227-1237. doi: 10.1016/j.jaad.2022.08.036.

2. Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. *N Engl J Med*. July 2,2015;373(1):48-59. doi: 10.1056/NEJMoa1411481

3. Mittal S, Anderson KE. Erythropoietic protoporphyria and X-linked protoporphyria. In: UpToDate, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 9, 2024. Accessed April 17, 2024.

4. Scenesse (afamelanotide) product information, revised by Clinuvel, Inc.; December 2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2024.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ 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: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights 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, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html