▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

SCENESSE 16 mg implant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The implant contains 16 mg of afamelanotide (as acetate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implant.
Solid white to off-white rod approximately 1.7 cm in length and 1.5 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SCENESSE is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

4.2 Posology and method of administration

SCENESSE should only be prescribed by specialist physicians in recognised porphyria centres and administration should be performed by a physician trained and accredited by the marketing authorisation holder to administer the implant.

Posology

One implant is administered every 2 months prior to expected and during increased sunlight exposure. The overall duration of treatment is at the specialist physician's discretion (see sections 4.4 and 5.1).

Special populations

For patients with renal or hepatic impairment see sections 4.3 and 5.2.

Elderly population

Due to limited data in treatment of elderly patients, the use of afamelanotide is not recommended (see section 4.4).

Paediatric population

The safety and efficacy of afamelanotide in children and adolescents aged to 17 years have not yet been established.
No data are available.

Method of administration

For subcutaneous use.

Instruction for use

- Take the packed implant out of the refrigerator and allow the medicinal product to warm up to ambient temperature.
- Have the patient sit in a comfortable position or lie on his/her back with the upper part of the body slightly raised.
- Disinfect the skin above the supra-iliac crest.
- Anaesthetise the insertion area if deemed necessary and in consultation with the patient.
- Select a 14 gauge (1.6 mm inner diameter) catheter with needle.
- Mark 1.5 to 2 cm on the catheter shaft using surgical ink.
- Hold the catheter at its base using a sterile technique, pinch and hold the skinfold cranial to, or overlying the patient's supra-iliac crest with two fingers.
- With the bevel of the needle facing upwards, insert the catheter laterally 1.5 to 2 cm into the subcutaneous layer at a 30 to 45 degree angle to the skin surface in one continuous flowing movement.
- With the catheter in place, aseptically remove the implant from the vial.
- Remove the needle from within the catheter using a sterile technique.
- Transfer the implant to the outlet of the catheter.
- Using a suitable device (such as a stylet) gently push the implant down the full length of the catheter lumen.
- Apply some pressure to the insertion area with your finger while removing the stylet and the catheter.
- Confirm insertion of the implant by palpating the skin with subcutis cranial to/overlying the suprailiac crest until the implant is located. Always verify the presence of the implant, if in doubt of its presence, check whether the implant has remained in the catheter. If the implant has not been administered during the procedural steps described above, discard the implant and administer a new implant. Do not administer a new implant unless it has been unequivocally confirmed that the first one had not been inserted.
- Apply a small pressure dressing to the injection site.
- Observe the patient for 30 minutes to ensure that you will notice if the patient develops an allergic or hypersensitivity reaction (immediate type).

The implant can be surgically removed if needed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Presence of severe hepatic disease
- Hepatic impairment (see section 5.2)
- Renal impairment (see section 5.2)

4.4 Special warnings and precautions for use

Hypersensitivity

Uncommon occurrences of hypersensitivity reactions, including anaphylaxis, have been reported following administration of SCENESSE. Appropriate medical support measures should be readily available when SCENESSE is administered. If a serious hypersensitivity reaction occurs, appropriate medical treatment should be initiated, the implant should be removed if needed and further treatment with SCENESSE should be discontinued (see section 4.8).

Concomitant disorders not studied

Clinically significant disorders of the gastrointestinal, cardiovascular, respiratory, endocrine (including diabetes, Cushing's disease, Addison's disease, Peutz-Jeghers syndrome), neurological (including seizures) and haematological (especially anaemia) systems have not been evaluated.
A careful decision must be made whether to treat patients with any of these conditions with this medicinal product. If such patients are treated they must be monitored after each implant administration, including vital signs, routine haematology, and biochemistry.

Sun protection

It is recommended that sun protection measures routinely adopted by each patient to manage their photosensitivity related to EPP and in accordance with their skin type (Fitzpatrick scale) are maintained during treatment with this medicinal product.

Skin monitoring

Afamelanotide may induce darkening of pre-existing pigmentary lesions due to its pharmacological effect. A regular full body skin examination (every 6 months) is recommended to monitor all pigmentary lesions and other skin abnormalities.
If the skin changes noted are consistent with skin cancer or its precursors, or are ambiguous to the porphyria specialist, dermatology specialist consultation should be sought.
The two total full body skin examinations per year are intended to:
- detect early any skin cancers and their precursors induced by UV-exposure, as EPP patients can be expected to significantly increase their exposure to sunlight and UV light while on treatment with afamelanotide. EPP patients with fair skin may be more likely to request treatment and are more prone to developing UV light-associated skin changes, including cancer;
- detect and monitor changes in pigmentary lesions, thus allowing early detection of melanoma.

Special caution is warranted in patients with an
- individual or family history of melanoma (inclusive of *in-situ* melanoma, e.g. lentigo maligna) or suspected or confirmed susceptibility to cutaneous melanoma (CMM1, MIM #155600, synonyms: familial atypical mole-malignant melanoma syndrome, FAMMM; dysplastic naevus syndrome, DNS; B-K mole syndrome; CMM2 MIM #155601)

and/or an
- individual history of basal cell carcinoma, squamous cell carcinoma (inclusive of carcinoma *in situ*, e.g. Bowen's disease), Merkel cell carcinoma, or other malignant or premalignant skin lesions.

Long-term use

Long-term safety data for afamelanotide are limited.
The safety of this medicinal product has not been evaluated in clinical studies of duration longer than 2 years (see section 4.2).

Elderly

Since available data in treatment of the elderly are limited, afamelanotide should not be used in patients over 70 years of age. If such patients are treated they must be monitored after administration of every implant, including vital signs, routine haematology and biochemistry.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with this medicinal product.
Pharmacokinetic data for afamelanotide or any of its metabolites are very limited. As an oligopeptide with a short half-life, afamelanotide is expected to be rapidly hydrolysed into shorter peptide fragments and into its individual amino acids. However, due to the lack of data caution is warranted.

Patients taking substances which reduce coagulation, such as vitamin K antagonists (e.g. warfarin), acetylsalicylic acid and non-steroidal anti-inflammatory drug (NSAIDs) may experience increased bruising or bleeding at the site of implantation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential have to use effective contraception during treatment with SCENESSE and for a period of three months thereafter.

Pregnancy

There are no or limited amounts of data from the use of afamelanotide in pregnant women.
Animal studies are insufficient with respect to developmental toxicity (see section 5.3). A risk to newborns/infants cannot be excluded.
SCENESSE should not be used during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether afamelanotide or any of its metabolites are excreted in breast milk.
No clinical data are available on the use of afamelanotide in breastfeeding women.

A risk to newborns/infants cannot be excluded. SCENESSE should not be used during breastfeeding.

Fertility

There are no clinical data on the effects of afamelanotide on fertility. Animal studies have not shown any harmful effect on fertility and reproduction.

4.7 Effects on ability to drive and use machines

Afamelanotide has moderate influence on the ability to drive and use machines, especially within 72 hours of administration. Following administration of this medicinal product, somnolence, fatigue, dizziness, and nausea have been reported. Patients should not drive or use machines in case they are affected by these symptoms.

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from clinical studies in 425 patients.
The most commonly reported adverse reactions are nausea, experienced by approximately 19% of subjects who received treatment with this medicinal product, headache (20%), and implant site reactions (21%; mainly discolouration, pain, haematoma, erythema). In most cases these adverse reactions are reported to be mild in severity.

Uncommon occurrences of hypersensitivity reactions, including anaphylaxis, have been reported in association with SCENESSE treatment (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions reported during clinical studies conducted with afamelanotide are listed in the table below by MedDRA system organ class and frequency convention.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and rare (≥1/10,000 to <1/1,000).

System Organ Class	Very common	Common	Uncommon	Rare
Infections and infestations		Influenza Upper respiratory tract infection	Cystitis Folliculitis Gastrointestinal infection Gastroenteritis	Candida infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Melanocyte naevus	Haemangioma	
Blood and lymphatic system disorders				Leukopenia
Immune system disorders			Hypersensitivity, Anaphylaxis	
Metabolism and nutrition disorders			Decreased appetite Increased appetite	Hypercholesterolaemia
Psychiatric disorders			Depressed mood including depression Insomnia	Confusional state
Nervous system disorders	Headache	Dizziness Migraine Somnolence	Balance disorder Hyperaesthesia Lethargy Paraesthesia Poor quality sleep Presyncope Restless leg syndrome Syncope	Dysgeusia Post-traumatic headache
Eye disorders			Dry eye Eye pain Ocular hyperaemia Photophobia Presbyopia	Eyelid oedema
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders			Palpitations	Tachycardia
Vascular disorders		Flushing Hot flush	Haemorrhage Haematoma Hypertension	Diastolic hypertension
Respiratory, thoracic and mediastinal disorders			Sinus congestion	
Gastrointestinal disorders	Nausea	Abdominal pain including abdominal discomfort Diarrhoea Toothache Vomiting	Abdominal distension Defaecation disorders Dyspepsia Flatulence Gastroesophageal reflux disease Gastritis Irritable bowel syndrome Gingival pain Hypoaesthesia oral Lip swelling	Bowel movement irregularity Cheilitis Gingival discolouration Lip discolouration Lip oedema Tongue discolouration

System Organ Class	Very common	Common	Uncommon	Rare
Skin and subcutaneous tissue disorders		Ephelides Erythema Pigmentation disorder Pruritus Rash including rash vesicular, rash erythematous, rash papular and rash pruritic	Acne Dermatitis contact Dry skin Eczema Hair colour changes Hyperhidrosis Nail pigmentation Papule Photosensitivity reaction Pigmentation lip Post inflammatory pigmentation change Pruritus generalised Skin burning sensation Skin discolouration Skin exfoliation Skin hyperpigmentation Skin hypopigmentation Skin irritation Skin lesion Seborrhoea Urticaria	Lichen planus Vitiligo
Musculoskeletal and connective tissue disorders		Musculoskeletal pain including back pain, arthralgia, pain in extremity and groin pain	Joint stiffnes Muscle spasm Musculoskeletal stiffness Muscular weakness	Limb discomfort
Reproductive system and breast disorders			Breast tenderness Dysmenorrhoea Menstruation irregular	Libido decreased Menorrhagia Vaginal discharge
General disorders and administration site conditions		Asthenia Fatigue Implant site disorders including implant site bruising, implant site discolouration, implant site erythema, implant site haematoma, implant site haemorrhage, implant site hypersensitivity, implant site hypertrophy, implant site induration, implant site irritation, implant site mass, implant site oedema, implant site pain, implant site pruritus, implant site reaction, implant site swelling, implant site urticaria,	Chills Feeling hot Hangover Malaise Oedema peripheral Oedema mucosal	

System Organ Class	Very common	Common	Uncommon	Rare
		implant site vesicles, implant site warmth Influenza-like illness including cough, nasal congestion, nasopharyngitis, oropharyngeal pain, rhinitis Pain Pyrexia		
Investigations			Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatine phosphokinase increased Blood glucose increased Blood iron decreased Blood urine present Hepatic enzyme increased Liver function test abnormal Transaminases increased	Blood pressure diastolic increased Transferrin saturation decreased Weight increased
Injury, poisoning and procedural complications			Fall Wound	Procedural nausea Wound complication
Product issues			Device expulsion	

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

There are no data available on symptoms or treatment of overdose with afamelanotide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Emollients and protectives, protectives against UV-radiation for systemic use, ATC code: D02BB02

Mechanism of action

Afamelanotide is a synthetic tridecapeptide and a structural analogue of α-melanocyte stimulating hormone (α-MSH). Afamelanotide is a melanocortin receptor agonist and binds predominantly to the melanocortin-1 receptor (MC1R). Its binding lasts longer than that of α-MSH. This results in part from afamelanotide's resistance to immediate degradation by serum or proteolytic enzymes (see section 5.2). It presumably undergoes hydrolysis within a short time; its metabolites' pharmacokinetics and pharmacodynamics are not understood yet.
Afamelanotide is thought to mimic the endogenous compound's pharmacological activity by activating the synthesis of eumelanin mediated by the MC1R receptor.
Eumelanin contributes to photoprotection through different mechanisms including:

- strong broadband absorption of UV and visible light, where eumelanin acts as a filter
- antioxidant activity through scavenging of free radicals; and
- inactivation of the superoxide anion and increased availability of superoxide dismutase to reduce oxidative stress.

Pharmacodynamic effects

Administration of afamelanotide may, therefore, result in increased production of eumelanin in the skin of the EPP patient independently of exposure to sunlight or artificial UV light. This can be accompanied by a darkening of the skin pigmentation in areas with melanocytes which gradually fades unless a further implant is administered.

Clinical efficacy and safety

From the clinical development programme, there are limited data on dosing 4-6 implants/year.

In the pivotal clinical trial CUV039 a total of three 16 mg SCENESSE implants were administered at a two-month interval. It has been demonstrated that EPP patients receiving afamelanotide had more exposure to direct sunlight (10:00 to 18:00 hours) during a 180 day trial period compared to placebo recipients (p=0.044; afamelanotide arithmetic mean: 115.6 h, median 69.4h; placebo mean 60.6h, median 40.8h).

In the supportive study CUV029 and a Post-Authorization Safety Study (PASS), five or up to six 16 mg SCENESSE implants were administered per year (at a two-month interval). The observed safety profile appears similar to that of the pivotal study CUV039.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with SCENESSE in one or more subsets of the paediatric population in erythropoietic protoporphyria (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Dose-finding studies have not been conducted.
The pharmacokinetics of afamelanotide have not been fully characterised yet, i.e. distribution, metabolism or excretion are not clear. No pharmacokinetic information is available on any of its metabolites (active or inactive).
Half-life is approximately 30 minutes.
Following subcutaneous administration of the implant, most of the active substance is released within the first 48 hours with over 90% released by day 5. Plasma levels of afamelanotide are maintained

over a number of days. In most clinical studies afamelanotide plasma levels were below the limit of quantitation by day 10. The implant is absorbed by the body within 50 to 60 days after administration.

Data on possible interactions or effects in special populations, e.g. in patients with hepatic or renal impairment are not available.

Paediatric population

No data are available.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.

In repeated dose toxicity studies, the only finding of relevance was an increase in melanin pigmentation in the dog, which is consistent with the active substance's pharmacological activity. This effect was observed only at exposure levels approximately 8 times higher than human exposure. Inflammation was observed in the Harderian gland in the rat. This finding is not considered relevant to human safety since the Harderian gland is not present in man.

In a fertility study no effects on the reproductive function of male or female Sprague-Dawley rats were observed after subcutaneous application of afamelanotide. A study in Sprague-Dawley rats showed no adverse effects on embryo-fetal development at exposures approximately 135-fold the human exposure (based on C_{max}). A second study on embryo-fetal development in Lister-Hooded rats did not achieve sufficient exposure. Pre- and post-natal development of Sprague-Dawley rats was not affected at exposures of about 135-times the human exposure (based on C_{max}).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly (DL-lactide-co-glycolide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

54 months.

6.4 Special precautions for storage

Store in a refrigerator (2˚C - 8˚C)

6.5 Nature and contents of container

Type I amber glass vial sealed with a PTFE coated rubber stopper.
Pack of one vial containing one implant.

6.6 Special precautions for disposal and other handling

For instructions on correct administration and preparation see section 4.2.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CLINUVEL EUROPE LIMITED
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/969/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 December 2014
Date of latest renewal: 19 November 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.