Product Information
SCENESSE®

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.
For further information on the scheme, see the Information for sponsors on the TGA website.

AUSTRALIAN PRODUCT INFORMATION
SCENESSE® afamelanotide Implant for subcutaneous use

1 NAME OF THE MEDICINE

Afamelanotide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SCENESSE® (afamelanotide) implant is a controlled-release dosage form for subcutaneous administration. The active ingredient is afamelanotide acetate. Each SCENESSE® implant contains 16 mg of afamelanotide (equivalent to 18 mg of afamelanotide acetate), and 15.3-19.5 mg of polyglactin.

For the full list of excipients, see Section 6.1 List of excipients

3 PHARMACEUTICAL FORM

SCENESSE® implant is a single, rod-shaped, solid white to off-white, bioresorbable and sterile implant approximately 1.7 cm in length and 1.45 mm in diameter. The implant core is comprised of the drug substance admixed with a polyglactin bioresorbable copolymer.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

SCENESSE must only be initiated by a specialist physician having expertise in the management of Erythropoietic Protoporphyria (EPP).

SCENESSE should be administered by a healthcare professional. All healthcare professionals should be proficient in the subcutaneous implantation procedure and have completed the training program provided by CLINUVEL prior to administration of the SCENESSE® implant.

A single SCENESSE® 16 mg implant is inserted subcutaneously above the anterior supra-iliac crest every 2 months.

Product Information
SCENESSE®

Method of administration

For subcutaneous use.

Instruction for use

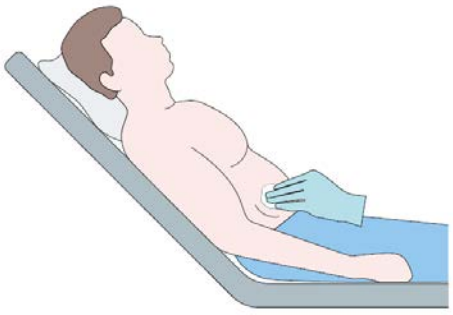
Insert a single SCENESSE implant (containing 16 mg of afamelanotide) subcutaneously above the anterior supra-iliac crest.

Implant SCENESSE observing an aseptic technique. The following equipment is needed for the implant insertion:

- SCENESSE implant
- A 14 gauge (1.6 mm inner diameter) catheter with needle. Alternatively, a trocar and obturator of similar dimension can be used
- Sterile gloves
- Local anaesthetic, needle and syringe
- Blunt forceps suitable for removing the SCENESSE implant from the glass vial and placement of the SCENESSE implant
- Sterile gauze, adhesive bandage, pressure bandage

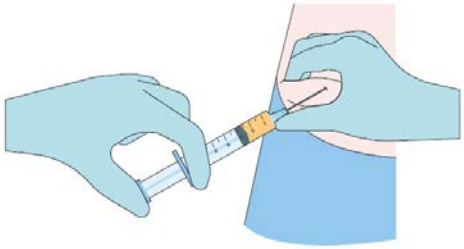
Step 1

Take the carton containing SCENESSE out of the refrigerator to allow the product to gradually warm up to ambient temperature.
Remove the seal and stopper from the glass vial containing SCENESSE. Use your hand to grasp the outer edge of the locking ring. Pull upwards using light to moderate force. Once the locking ring is removed, flip off the rubber stopper.
Remove the implant from the vial using the blunt forceps under aseptic conditions and place the implant on a sterile gauze.



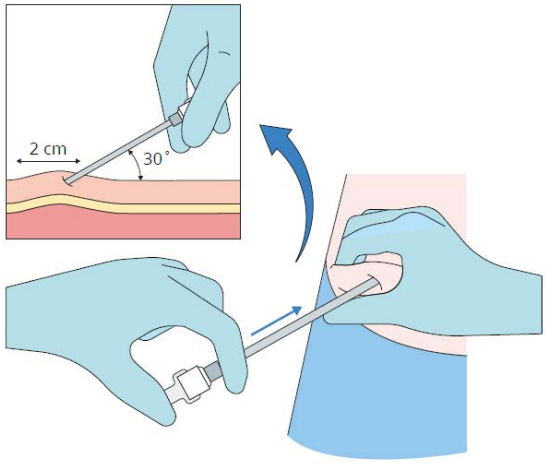
Step 2

Put the patient in a comfortable reclined supine position. Identify the insertion site 3-4 cm above the anterior supra-iliac crest and disinfect the skin surface.

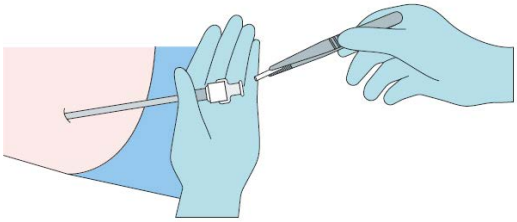


Step 3 (optional)

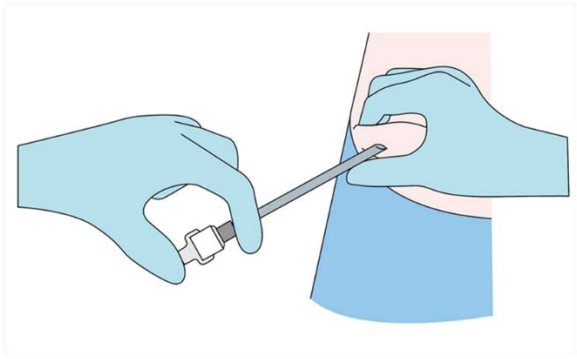
Anesthetize the area of insertion (puncture) if deemed necessary and in consultation with the patient.



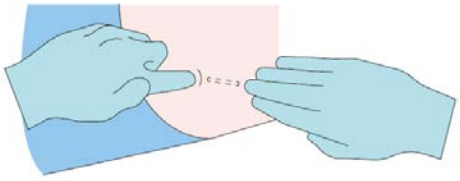
Step 4
While pinching the skin of the insertion site, insert the catheter/trocar with the bevel facing upwards (away from the abdomen) at a 30-45° angle into the subcutaneous layer. Advance the catheter/trocar 2 cm into the subcutaneous layer.



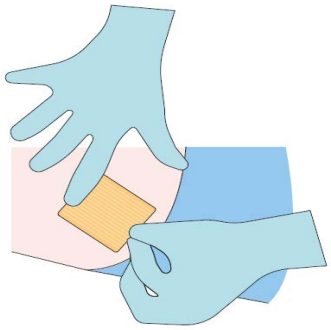
Step 5
Remove the needle/obturator from the catheter/trocar sleeve maintaining aseptic precautions.
Load the implant into the catheter/trocar sleeve.
Using the needle/obturator gently push the implant down the full length of the catheter/trocar lumen.



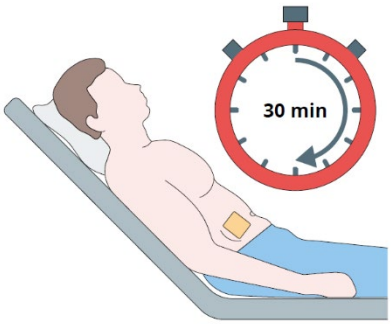
Step 6
Apply some pressure to the site of the implant while removing the needle/obturator and the catheter/trocar sleeve. Verify that no implant or implant portion remains in the catheter/trocar sleeve.



Step 7
Verify the correct insertion and placement of the implant by palpating the skin overlying the implant with two fingers.



Step 8
Apply dressing to the insertion site. Leave dressing in place for 24 hours.



Step 9
Monitor the patient for 30 minutes after the implant administration.

The implant can be surgically removed if needed. If it is necessary, implant removal is recommended within 96 hours of implantation.

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 4.4)
- Renal impairment (see section 4.4)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Use in the 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.

Paediatric use

The safety and efficacy of afamelanotide in children and adolescents aged 0 to 17 years have not yet been established.

Effects on laboratory tests

No data available.

Long-term use

Long-term safety data for afamelanotide are limited.

The safety of this medicinal product has not been evaluated in clinical trials of duration longer than 2 years (see section 5.1).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies were conducted with afamelanotide.

Inhibition of CYP enzymes and transporters by afamelanotide is not expected, nor for such inhibition to affect the pharmacokinetics of afamelanotide.

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

Effects on fertility

There are no clinical data on the effects of afamelanotide on fertility. No effects on male or female fertility were observed with afamelanotide in rats at subcutaneous doses up to 20 mg/kg/day (12 times the maximum recommended human dose, based on body surface area comparison).

Use in pregnancy – Category B1

There are no or limited amounts of data from the use of afamelanotide in pregnant women.

No adverse effects on embryofoetal development were observed with afamelanotide in rats (albino and pigmented strains) at subcutaneous doses up to 20 mg/kg/day (12 times the maximum recommended human dose, based on body surface area comparison).

SCENESSE® should only be used during pregnancy, and for a period of three months following discontinuation of treatment, if the benefit to the mother outweighs the potential risk to the foetus.

Use in lactation

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.

Use of SCENESSE® during breastfeeding should consider the developmental and health benefits of breastfeeding, the clinical need of the mother, and the potential for adverse effects in the newborn/infant.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

The majority of subjects in both active and placebo groups experienced at least one Treatment Emergent Adverse Event (TEAE). For the majority of these subjects, the greatest severity of any TEAE was mild or moderate. In both groups, fewer than 50% reported any TEAE that was considered to be related to study drug.

Table 1 below presents a summary of the most common events (≥ 5%) observed in both afamelanotide and placebo groups. The most frequently observed AEs across patient populations were headache, nausea, nasopharyngitis, back pain and influenza.

Table 1

Preferred term	Number (%) of Subjects, Number of Events	
	All Studies Active (N=230)**	**All Studies** Placebo (N=219)**
Any event		
Headache	87 (38%) 258	75 (34%) 251
Nausea	60 (26%) 107	35 (16%) 53
Nasopharyngitis	41 (18%) 46	36 (16%) 43
Back pain	23 (10%) 34	21 (9.6%) 43
Influenza	23 (10%) 25	15 (6.8%) 17
Diarrhoea	20 (8.7%) 25	22 (10%) 28
Fatigue	19 (8.3%) 30	14 (6.4%) 30
Dizziness	17 (7.4%) 23	9 (4.1%) 32
Abdominal pain	16 (7.0%) 20	11 (5.0%) 14
Oropharyngeal pain	14 (6.1%) 16	16 (7.3%) 24
Implant site pain	14 (6.1%) 15	13 (5.9%) 15
Migraine	13 (5.7%) 38	15 (6.8%) 32
Implant site discolouration	13 (5.7%) 16	0 (0.0%) 0
Cough	12 (5.2%) 13	13 (5.9%) 16
Arthralgia	10 (4.3%) 14	12 (5.5%) 22
Toothache	8 (3.5%) 11	12 (5.5%) 16
Sinusitis	6 (2.6%) 6	12 (5.5%) 18

** Integrated Summary of Safety population: CUV010, CUV017, CUV029, CUV030 and CUV039

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.

Tabulated list of adverse reactions

The adverse reactions reported during clinical trials conducted with afamelanotide are listed in Table 2 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), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 2

System Organ Class	Very common	Common	Uncommon
Infections and infestations		Upper respiratory tract infection	Influenza Gastrointestinal infection Gastroenteritis Folliculitis Candidiasis Nasopharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Haemangioma
Blood and lymphatic system disorders			Leukopenia
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia Increased appetite
Psychiatric disorders			Depression Depressed mood Insomnia
Nervous system disorders	Headache	Migraine Dizziness Lethargy Somnolence	Syncope Restless leg syndrome Hyperaesthesia Presyncope Post-traumatic headache Burning sensation Poor quality sleep Dysgeusia
Eye disorders			Eyelid oedema Ocular hyperaemia Dry eye Presbyopia
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Palpitations Tachycardia
Vascular disorders		Flushing Hot flush	Haematoma Diastolic hypertension Hypertension

System Organ Class	Very common	Common	Uncommon
Respiratory, thoracic and mediastinal disorders			Dysphonia Sinus congestion Rhinitis Nasal congestion
Gastrointestinal disorders	Nausea	Abdominal pain Abdominal pain upper Diarrhoea Vomiting	Lip oedema Lip swelling Gastroesophageal reflux disease Gastritis Dyspepsia Cheilitis Abdominal distension Gingival pain Abdominal discomfort Toothache Abdominal symptom Bowel movement irregularity Flatulence Gingival discolouration Hypoaesthesia oral Lip discolouration Tongue discoloration
Skin and subcutaneous tissue disorders		Erythema Melanocytic naevus Pigmentation disorder Skin discolouration Skin hyperpigmentation Ephelides Pruritus	Lichen planus Rash vesicular Pruritus generalised Rash Rash erythematous Rash papular Rash pruritic Skin irritation Vitiligo Acne Eczema Pigmentation lip Post inflammatory pigmentation change Seborrhoea Skin exfoliation Skin hypopigmentation Hair colour changes Hyperhidrosis

System Organ Class	Very common	Common	Uncommon
Musculoskeletal and connective tissue disorders		Back pain	Arthralgia Myalgia Pain in extremity Muscle spasm Musculoskeletal pain Musculoskeletal stiffness Joint stiffness Groin pain Sensation of heaviness
Renal and urinary disorders			Cystitis
Reproductive system and breast disorders			Menorrhagia Dysmenorrhoea Breast tenderness Menstruation irregular Vaginal discharge Libido decreased
General disorders and administration site conditions		Implant site hypersensitivity Implant site reaction Implant site pain Implant site haematoma Implant site erythema Implant site irritation Asthenia Fatigue Implant site discolouration Feeling hot	Oedema peripheral Oedema mucosal Pain Implant site oedema Pyrexia Chills Injection site haematoma Injection site irritation Implant site hypertrophy Implant site pruritus Device expulsion Application site discolouration Hangover Influenza like illness
Investigations		Blood creatine phosphokinase increased	Alanine aminotransferase increased Aspartate aminotransferase increased Liver function test abnormal Transaminases increased Transferrin saturation decreased Blood cholesterol increased

System Organ Class	Very common	Common	Uncommon
			Blood glucose increased Blood iron decreased Blood pressure diastolic increased Blood urine present Biopsy skin
Injury, poisoning and procedural complications			Wound complication Open wound Fall Procedural nausea

Post-marketing Experience

Marketing authorisation was obtained in the European Union in December 2014. SCENESSE® has been commercially distributed in Europe, predominantly via a post-authorisation safety study (PASS)/ disease registry study, and partly through an expanded access program in Switzerland and Italy. All treating physicians within the European Union follow a treatment protocol which mandates reporting of adverse reactions.

Adverse reactions reported to CLINUVEL under these programs are listed in Table 3 and include data obtained from approximately 1,200 SCENESSE® administrations. Given the limited clinical use of SCENESSE® in a relatively small patient population since obtaining marketing authorisation in Europe, the reported adverse reaction incidence should be regarded as preliminary at this time.

Table 3

System Organ Class	Very common	Common	Uncommon
Infections and infestations			Influenza Viral upper respiratory tract infection
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders			Insomnia
Nervous system disorders	Headache	Dizziness Somnolence	Dysgeusia Migraine
Ear and labyrinth disorders			Tinnitus
Vascular disorders		Flushing Hot flush	Haematoma
Gastrointestinal disorders	Nausea		Abdominal distension Abdominal discomfort Abdominal pain

System Organ Class	Very common	Common	Uncommon
			Abdominal pain upper Diarrhoea Dyspepsia
Skin and subcutaneous tissue disorders		Pigmentation disorder	Acne Erythema Hyperhidrosis Pruritus Pigmentation lip Rash Seborrhoea
General disorders and administration site conditions		Asthenia Fatigue Implant site pain	Feeling hot Implant site discoloration Implant site haematoma Implant site haemorrhage Implant site pruritus Influenza like illness Malaise Pain

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no data available on symptoms or treatment of overdose with afamelanotide.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 (MC1-R). It acts with 4-fold greater potency than

α-MSH *in vitro* and, due to increased resistance to proteolysis, has a longer duration of action *in vivo*.

Activation of the MC1-R receptor by afamelanotide stimulates the synthesis of eumelanin in melanocytes.

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.

Clinical trials

Five clinical studies were undertaken to establish the safety and effectiveness of SCENESSE® in patients with EPP. These included a pilot study, a study involving a multiple crossover (alternating active and placebo) design and three placebo-controlled studies.

The three placebo-controlled trials of SCENESSE® were conducted in subjects with EPP. Of these trials, two trials (Study CUV039 and Study CUV029) were designed to assess exposure to direct sunlight on days with no phototoxic pain. The two trials differed in the number of days of follow-up, the time windows within a day in which time spent outdoors was recorded, and how the amount of time spent in direct sunlight on each day was characterised. The subjects enrolled in these trials were primarily Caucasian (98%), the mean age was 40 years (range 18 to 74 years), and 53% of subjects were male and 47% were female.

Study CUV039 enrolled 93 subjects, of whom 48 received SCENESSE® (16 mg of afamelanotide administered subcutaneously every 2 months), 45 received vehicle. Subjects received three implants and were followed for 180 days. On each study day, subjects recorded the number of hours spent in direct sunlight and in shade (between10am and 6pm), and whether they experienced any phototoxic pain that day. The primary endpoint was the total number of hours spent in direct sunlight on days with no pain, over 180 days. The median total number of hours spent in direct sunlight on days with no pain was 64.1 hours for subjects receiving SCENESSE® and 40.5 hours for subjects receiving placebo.

Study CUV029 enrolled 74 subjects, of whom 38 received SCENESSE® (16 mg of afamelanotide administered subcutaneously every 2 months), 36 received vehicle. Subjects received five implants and were followed for 270 days. On each study day, subjects recorded the number of hours spent in direct sunlight, shade, or a combination of both (between 10am and 3pm), and whether they experienced any phototoxic pain that day. The primary endpoint was the total number of hours over 270 days spent outdoors with no pain for which “most of the day” was spent in direct sunlight. The median total number of hours over 270 days spent outdoors on days with no pain for which “most of the day” was spent in direct sunlight was 6.0 hours for subjects in the SCENESSE® group and 0.75 hours for subjects in the placebo group.

There is no clinical evidence to determine whether SCENESSE is protective against long term effects of phototoxicity such as scarring or skin changes resulting from exposure to light.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of afamelanotide following administration of a single subcutaneous implant of SCENESSE® were evaluated in 12 healthy adults. High variability was observed in the plasma concentrations of afamelanotide and for most subjects (9 out of 12), the last measurable afamelanotide concentration was at 96 hours post-dose. The mean ± SD C_{max} and $AUC_{0\text{-}inf}$ were 3.7 ± 1.3 ng/mL and 138.9 ± 42.6 hr*ng/mL, respectively.

Absorption

The median T_{max} following implant administration was 36 hr.

Metabolism

Afamelanotide is degraded into smaller peptide fragments by hydrolysis and not via oxidative metabolism by CYP enzymes.

Excretion

The apparent half-life of afamelanotide is approximately 15 hr when administered subcutaneously in a controlled release implant. Peptide fragments of afamelanotide are excreted renally.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Afamelanotide was negative for genotoxicity in the bacterial reverse mutation assay (Ames test), *in vitro* mouse lymphoma assay, and *in vivo* mouse bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with afamelanotide. *In vitro*, afamelanotide was shown not to stimulate cell proliferation in cultured human melanoma cells expressing MC1-R.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polyglactin

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2°C – 8°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

SCENESSE® (afamelanotide) implant, 16 mg, for subcutaneous administration is supplied in a Type I amber glass vial sealed with a PTFE coated rubber stopper. Each vial contains one afamelanotide implant and is packaged individually in a cardboard box.

SCENESSE® implants are not supplied with an implantation device for subcutaneous administration [see *Dosage and Administration*].

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For instructions on correct administration and preparation see section 4.2.

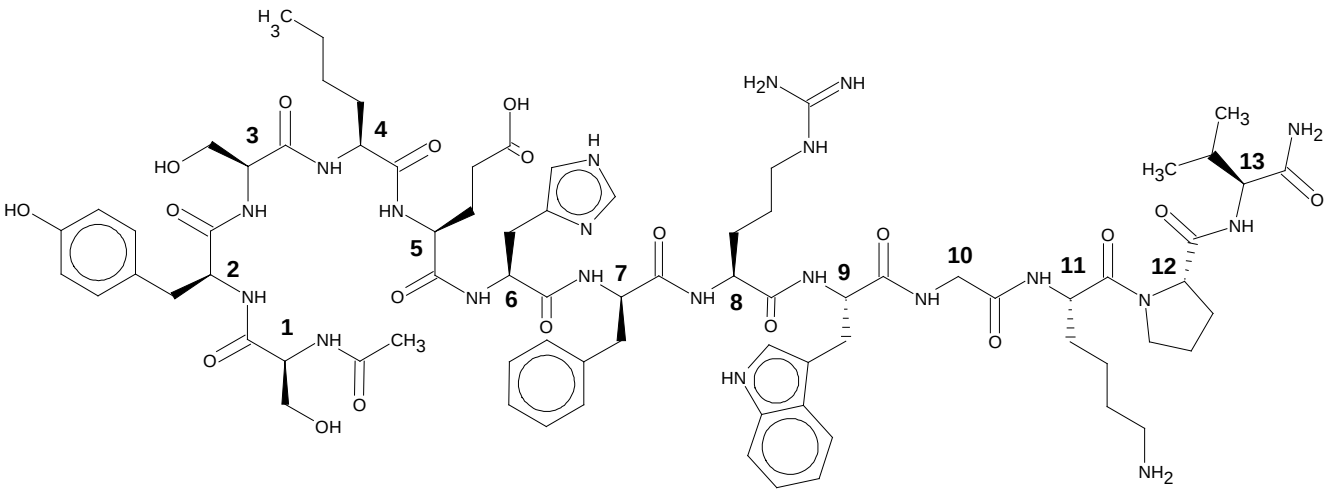
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Ac-Ser-Tyr-Ser-Nle-Glu-His-(D)Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

1 2 3 4 5 6 7 8 9 10 11 12 13



CAS number

75921-69-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

22 October 2020

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
n/a	