SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Luxera 160 mg/g cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Luxera contains 160 mg/g of methyl aminolevulinate (as hydrochloride) equivalent to 16.0% of methyl aminolevulinate (as hydrochloride).

Excipients with known effect:
Luxera contains cetostearyl alcohol (40 mg/g), methyl parahydroxybenzoate (E 218; 2 mg/g), propyl parahydroxybenzoate (E 216; 1 mg/g) and arachis oil (30 mg/g).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.
The colour is cream to pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AKs) on the face and scalp.
Luxera is indicated in adults above 18 years of age.

4.2 Posology and method of administration

Posology

Adults (including the older people)

AK using daylight
One session of daylight photodynamic therapy should be administered to treat mild to moderate AKs lesions and/or field cancerization. Treated lesions should be evaluated after three months and if there has been an incomplete response, a second treatment may be given.

Paediatric population

The safety and efficacy of Luxera in children below 18 years have not yet been established.

Method of administration

a) *Considerations before treatment*: Luxera can be used if the temperature conditions are suitable to stay comfortably outdoors for 2 hours. If the weather is rainy, or is likely to become so, Luxera should not be used.

b) *Preparation of the lesions:* A sunscreen should be applied, please see section 4.4. Once sunscreen has dried, scales and crusts should be removed and the skin surface roughened before applying a thin layer of Luxera to the lesion (s) or field of cancerization. No occlusion is necessary.

c) *Illumination:* Patients should go outside after Luxera application or, at the latest, 30 minutes later in order to avoid excessive protoporphyrin IX accumulation which would lead to greater pain on light exposure. In order to minimize pain and ensure maximum efficacy the patient should then stay outdoors for 2 continuous hours in full daylight and avoid going indoors. On sunny days, should the patient feel uncomfortable in direct sunlight, shelter in the shade from time to time may be taken. Following the 2-hour exposure period, Luxera should be washed off.

Multiple lesions may be treated during the same treatment session.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, including arachis oil or peanut or soya.
Porphyria.

4.4 Special warnings and precautions for use

A sunscreen should be applied to all areas exposed to daylight, including the treatment areas, prior to lesion preparation. Sunscreen used should offer adequate protection (SPF30 or higher) and must not include physical filters (e.g. titanium dioxide, zinc oxide, iron oxide) as these inhibit absorption of visible light which may impact efficacy. Only sunscreens with chemical filters should be used with daylight treatment.

Luxera is not recommended during pregnancy (see section 4.6).

Thick (hyperkeratotic) actinic keratoses should not be treated with Luxera. There is no experience of treating lesions which are pigmented, highly infiltrating or located on the genitalia with Luxera.

There is limited experience from post-authorisation exposure in treating actinic keratosis in transplant patients on immunosuppressive therapy. A close monitoring of these patients, with re-treatment if necessary is recommended in this population.

Methyl aminolevulinate may cause sensitization by skin contact resulting in angioedema, application site eczema or allergic contact dermatitis. The excipient cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis), methyl- and propyl parahydroxybenzoate (E218, E216) may cause allergic reactions (possibly delayed).

Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure of the treated lesion sites and surrounding skin should be avoided for about 2 days following treatment. Direct eye contact with Luxera should be avoided. Luxera cream should not be applied to the eyelids and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of methyl aminolevulinate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Luxera is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding
It is unknown whether methyl aminolevulinate/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Luxera therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Safety of methyl aminolevulinate (MAL) daylight photodynamic therapy (DL-PDT) was compared to conventional photodynamic therapy activated by red light (c-PDT) in two randomized, investigator-blinded, comparative, intra-individual clinical studies conducted in Australia and Europe, including a total of 231 patients. Patients were treated for actinic keratoses on one side of the face or scalp with MAL DL-PDT and on the contralateral side with MAL c-PDT. No new local adverse reactions were reported in these two phase III studies compared to the already known local adverse reactions with MAL c-PDT. Luxera (DL-PDT) was almost painless compared to MAL c-PDT (refer to section 5.1). In the two Phase III studies, local related adverse events were reported less frequently on Luxera treated side (DL-PDT) compared to MAL c-PDT treated side (45.0% and 60.1% of subjects, respectively).

Luxera is indicated only for the treatment of actinic keratoses (AK). MAL c-PDT is used in the treatment of AK, basal cell carcinoma (BCC) and Bowen's disease and the incidence of adverse reactions in these 3 indications is listed below.
Tabulated list of adverse reactions with MAL c-PDT: the incidence of adverse reactions in a clinical trial population of 932 patients with AKs, BCC and Bowen's disease receiving the treatment regimen with red light and adverse reactions reported from the post marketing surveillance are shown in Table 1 below.
The adverse reactions are classified by System Organ Class and frequency, using the following convention: 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), not known (cannot be estimated from the available data) (see Table 1).

Table 1: tabulated list of adverse reactions of MAL c-PDT (activated by red light)

System organ class (MedDRA)	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Paraesthesia, headache
Eye disorders	Uncommon	Eye swelling, eye pain
	Not known	Eyelid oedema
Vascular disorders	Uncommon	Wound haemorrhage
	Not known	Hypertension
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Very common	Pain of skin, skin burning sensation, scab, erythema
	Common	Skin infection, skin ulcer, skin oedema, skin swelling, blister, skin hemorrhage, pruritus, skin exfoliation, skin warm
	Uncommon	Urticaria, rash, skin irritation, photosensitivity reaction, skin hypopigmentation, skin hyperpigmentation, heat rash, skin discomfort
	Not known	Angioedema, face oedema (swelling face), application site eczema, allergic contact dermatitis, rash pustular (application site pustule)
General disorders and	Common	Application site discharge, feeling hot

administration site conditions	Uncommon	Fatigue

Reporting of suspected adverse reactions
Reporting 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

The severity of local phototoxic reactions such as erythema, pain and burning sensation may increase in case of prolonged application time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, ATC Code: L01X D03

Mechanism of action
After topical application of methyl aminolevulinate, porphyrins are produced intracellularly in the treated skin lesions. The intracellular porphyrins (including PpIX) are photoactive, fluorescing compounds and, upon daylight activation in the presence of oxygen, singlet oxygen is formed which causes damage to cellular compartments, in particular the mitochondria. PpIX is continuously being produced and activated within the target cells during the 2 hours of daylight exposure creating a constant micro-phototoxic effect. There may not be sufficient daylight during winter months in certain parts of Europe for Luxera treatment. Luxera therapy is feasible all year long in southern Europe, from February to October in middle Europe, and from March to October in northern Europe.

Clinical efficacy
The efficacy and safety of methyl aminolevulinate (MAL) daylight photodynamic therapy (DL-PDT) was compared to conventional photodynamic therapy activated by red light (c-PDT) in two randomised, investigator-blinded, comparative, intra-individual clinical studies conducted in Australia and Europe, including a total of 231 patients. Patients were treated on one side of the face or scalp with MAL DL-PDT and on the contralateral side with MAL c-PDT.
The results of both Phase III studies demonstrated that MAL DL-PDT is similar (non-inferior) to MAL c-PDT for treating AK lesions (on the percentage change from baseline in the number of treated lesions per side at 12 weeks after one treatment) and is significantly less painful.
In the Australian study, the percentage change from baseline in the number of mild treated lesions was 89.2% versus 92.8% for DL-PDT versus c-PDT respectively (95% CI of the mean treatment difference: [-6.8; -0.3], per protocol population). In the European study, the percentage change from baseline in the number of total (mild and moderate) treated lesions was 70.1% versus 73.6% for DL-PDT versus c-PDT respectively (95% CI of the mean treatment difference: [-9.5; 2.4], per protocol population).
MAL DL-PDT was almost painless compared to MAL c-PDT, with a pain score (on an 11-point scale ranging from 0 to 10) of 0.8 versus 5.7 ($p<0.001$) in the Australian study and 0.7 versus 4.4 ($p<0.001$) in the European study.
In both studies, regardless of whether the weather was sunny or cloudy, efficacy was demonstrated.
The maintenance of lesion response rate assessed in the Australian study was high with both treatments for patients presenting at week 24 (96% for DL-PDT and 96.6% for c-PDT).

5.2 Pharmacokinetic properties

In vitro dermal absorption of radiolabelled methyl aminolevulinate applied to human skin has been studied. After 24 hours the mean cumulative absorption through human skin was 0.26% of the administered dose. A skin depot containing 4.9% of the dose was formed. No corresponding studies in

human skin with damage similar to actinic keratosis lesions and additionally roughened surface or without stratum corneum were performed.
In humans, a higher degree of accumulation of porphyrins in lesions compared to normal skin has been demonstrated with MAL cream. When using Luxera, photobleaching occurs continuously during the 2 hours of daylight exposure (refer to section 5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. When methyl aminolevulinate was administered by IV at high dose levels during gestation, studies in animals showed reproductive toxicity. Findings included effects on ossification in rabbits and a slightly longer gestation duration in rats. As a result, methyl aminolevulinate should be avoided during pregnancy in humans.
Carcinogenicity studies have not been performed with methyl aminolevulinate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Self-emulsifying glyceryl monostearate
cetostearyl alcohol
poloxyl 40 stearate
methyl parahydroxybenzoate (E 218)
propyl parahydroxybenzoate (E 216)
disodium edetate
glycerol
white soft paraffin
cholesterol
isopropyl myristate
arachis oil
refined almond oil
oleyl alcohol
purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 15 months.
3 months after first opening of the container.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

Aluminium tube with internal protective lacquer and a latex seal. Screw cap of HDPE.
Luxera cream is supplied in a tube containing 2 g cream.

6.6 Special precautions for disposal <and other handling>

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2022-09-12

<Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}>