Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metvix 160 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Metvix 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 on the face and scalp.
Only for treatment of superficial and/or nodular basal cell carcinoma unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome; such as lesions on the mid-face or ears, lesions on severely sun damaged skin, large lesions, or recurrent lesions.
Treatment of squamous cell carcinoma in situ (Bowen´s disease) when surgical excision is considered less appropriate.
Metvix is indicated in adults above 18 years of age.

4.2 Posology and method of administration

Posology
Adults (including the older people)

AK, BCC and Bowen's disease using red light
For treatment of actinic keratoses (AK) one session of photodynamic therapy should be administered. Treated lesions should be evaluated after three months and if there has been an incomplete response, a second treatment may be given. For treatment of basal cell carcinoma (BCC) and Bowen's disease two sessions should be administered with an interval of one week between sessions. Before applying Metvix, the lesion surface should be prepared to remove scales and crusts and roughen the surface of the lesions. Nodular BCC lesions are often covered by an intact epidermal keratin layer which should be removed. Exposed tumour material should be removed gently without any attempt to excise beyond the tumour margins.

AK using daylight
The daylight treatment may be used to treat mild to moderate AK lesions. One treatment should be given. 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 Metvix in children below 18 years have not yet been established.

Method of administration
Treatment of AKlesions and/or field cancerization, BCC and Bowen's disease using red-light lamp:
Preparation of the lesions: Scales and crusts should be removed, and the skin surface roughened before applying a thin layer of Metvix to the lesion(s). Using a spatula, apply a layer of Metvix (about 1 mm thick) to the lesion lesion area (for field

cancerization up to 20 cm^2, approximately) and approximately 5-10 mm of the surrounding area. Cover the treated area with an occlusive dressing for 3 hours.

1. Remove the dressing and clean the area with saline. *Illumination:* Immediately after cleaning the lesions, the entire treatment area will be illuminated with a red-light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm^2 or a broader and continuous spectrum in a range between 570 and 670 nm with a light dose of approximately 75 J/cm^2. The light intensity at the lesion surface should not exceed 200 mW/cm^2.Only CE marked lamps should be used, equipped with necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation. It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. The light dose delivered should be monitored if a suitable detector is available.
2. Patient and operator should adhere to safety instructions provided with the light source. During illumination patient and operator should wear protective goggles which correspond to the lamp light spectrum. Healthy untreated skin surrounding the lesion does not need to be protected during illumination. Multiple lesions may be treated during the same treatment session.Lesion responses should be assessed after three months, and at this response evaluation, lesion sites showing non-complete response may be retreated if desired. It is recommended that the response of BCC and Bowen's disease lesions be confirmed by histological examination of biopsy material. Subsequently, close long term clinical monitoring of BCC and Bowen´s disease is recommended, with histology if necessary.

Treatment of AK lesions and/or field cancerization withnatural daylight

a) Considerations before treatment: Metvix natural daylight treatment 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, Metvix natural daylight treatment should not be used (see section 5.1).
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 Metvix to the lesion(s) or field of cancerization. No occlusion is necessary.
c) Illumination using daylight for AK treatment: Patients should go outside after Metvix 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 natural daylight and avoid going indoors. On sunny days, should the patient feel uncomfortable in direct sunlight, shelter in the shade may be taken. Following the 2 hour exposure period, Metvix should be washed off.

Multiple lesions may be treated during the same treatment session.

Treated lesions should be evaluated after three months and if there has been an incomplete response, a second treatment may be given.

Treatment of AK lesions and/or field cancerization using artificial daylight device

Preparation of the lesions: Scales and crusts should be removed, and the skin surface roughened before applying a thin layer of Metvix to the areas to be treated.
a) Occlusion is not necessary. Sunscreen is not needed, as patients are not exposed to ultraviolet light.

Illumination using artificial daylight for AK treatment: Lesion should be exposed after Metvix 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 be exposed to artificial daylight for 2 continuous

hours in a comfortable position.

Following the 2-hour exposure period, Metvix should be washed off.

Only CE marked devices should be used. The devices should have a continuous light spectrum of 400 to 750 nm and an illuminance greater than 12,000 lux at the lesion surface. It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the illuminance (or equivalent), the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. Patient and operator should adhere to safety instructions provided with the light source.

b) Healthy untreated skin surrounding the lesion does not need to be protected during illumination. Multiple lesions may be treated during the same treatment session. Lesion responses should be assessed after three months, and at this response evaluation, lesion sites showing incomplete response may be retreated if desired.

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.
Morpheaform basal cell carcinoma.
Porphyria.

4.4 Special warnings and precautions for use

The usage of Metvix requires a specific knowledge in photodynamic therapy as it may necessitate the use of a red-light lamp or an artificial daylight lamp. Accordingly, it should be administered in the presence of a physician, a nurse or other health care professional trained in the use of photodynamic therapy.

When using Metvix with natural daylight, 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 (eg. 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.

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

Thick (hyperkeratotic) actinic keratoses should not be treated with Metvix. There is no experience of treating lesions which are pigmented, highly infiltrating or located on the genitalia with Metvix. There is no experience of treating Bowen´s disease lesions larger than 40 mm. As with cryotherapy and 5-FU therapy of Bowen´s disease, response rates of large lesions (>20 mm in diameter) are lower than those of small lesions.
There is limited experience from post-authorisation exposure in treating actinic keratoses and Bowen´s disease in transplant patients on immunosuppressive therapy. A close monitoring of these patients, with re-treatment if necessary is recommended in this population.
There is no experience of treating Bowen´s disease in patients with a history of arsenic exposure.

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 Metvix should be avoided. Metvix cream should not be applied to the eyelids and mucous membranes.

Pain during illumination with red light may induce increased blood pressure. It is thus recommended to measure blood pressure in all patients prior to treatment with red light. If severe pain occurs during treatment with red light, the blood pressure should be checked. In case of severe hypertension, the illumination with red light should be interrupted in addition to taking appropriate symptomatic measures.

Conventional Photodynamic Therapy (PDT) with a red-light lamp may be a precipitating factor for transient global amnesia in very rare instances. Although the exact mechanism is not known, stress and pain associated with illumination with the lamp may increase the risk to develop transient amnesia. If signs of confusion or disorientation are observed, PDT must be discontinued immediately

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).
Metvix 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 Metvix 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

Metvix with red light in AK, BCC and Bowen's disease
a) Summary of the safety profile: approximately 60% of patients experience reactions localised to the treatment site that are attributable to toxic effects of the photodynamic therapy (phototoxicity) or to preparation of the lesion.
The most frequent symptoms are painful and burning skin sensation typically beginning during illumination or soon after and lasting for a few hours with resolving on the day of treatment. The symptoms are usually of mild or moderate severity and rarely require early termination of illumination. The most frequent signs of phototoxicity are erythema and scab. The majority are of mild or moderate severity and persist for 1 to 2 weeks or occasionally longer.
Local phototoxic reactions may be reduced in frequency and severity with repeated treatment of Metvix.

b) Tabulated list of adverse reactions: the incidence of adverse reactions in a clinical trial population of 932 patients receiving the standard treatment regimen with red light and adverse reactions reported from the post marketing surveillance are shown in the table 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

System organ class (MedDRA)	**Frequency***	**Adverse reaction**
Nervous system disorders	Common	Paraesthesia, headache
	Not Known	Transient global amnesia (including confusional state and disorientation)
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 administration site conditions	Common	Application site discharge, feeling hot
	Uncommon	Fatigue

Metvix with daylight in AK
No new local adverse reactions were reported in the two phase III Metvix daylight studies compared to the already known local adverse reactions with Metvix red light. Metvix DL-PDT was almost painless compared to Metvix c-PDT (refer to section 5.1). In the two Phase III studies, including a total of 231 patients, local related adverse events were reported less frequently on Metvix DL-PDT than on c-PDT treated sides (45.0% and 60.1% of subjects, respectively).

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 via HPRA Pharmacovigilance; Website: www.hpra.ie

4.9 Overdose

The severity of local phototoxic reactions such as erythema, pain and burning sensation may increase in case of prolonged application time and/or very high red-light intensity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, ATC Code: L01X D03

Mechanism of action

- Metvix with red light in AK, BCC and Bowen's diseaseAfter topical application of methyl aminolevulinate, porphyrins accumulate intracellularly in the treated skin lesions. The intracellular porphyrins (including PpIX) are photoactive, fluorescing compounds and, upon light activation in the presence of oxygen, singlet oxygen is formed which causes damage to cellular compartments, in particular the mitochondria. Light activation of accumulated porphyrins leads to a photochemical reaction and thereby phototoxicity to the light-exposed target cells.
- Metvix with daylight in AK 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. When Metvix is used with daylight, PpIX is continuously being produced and activated within the target cells during the 2 hours of daylight exposure creating a constant micro-phototoxic effect. Natural daylight may not be sufficient for Metvix daylight treatment during winter months in certain parts of Europe. Metvix natural daylight photodynamic therapy is feasible all year long in southern Europe, from February to October in middle Europe, and from March to October in northern Europe.Metvix photodynamic therapy with artificial daylight lamp is feasible all year long without any restriction.

Clinical efficacy

- Metvix with daylight in AK The efficacy and safety of Metvix daylight photodynamic therapy (DL-PDT) was compared to Metvix conventional photodynamic therapy (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 Metvix DL-PDT and on the contralateral side with Metvix c-PDT. The results of both Phase III studies demonstrated that Metvix DL-PDT is similar (non-inferior) to

Metvix 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).Metvix DL-PDT was almost painless compared to Metvix 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 Metvix cream. After application of the cream for 3 hours and subsequent illumination with non-coherent light of 570-670 nm wavelength and a total light dose of 75 J/cm^2, complete photobleaching occurs with levels of porphyrins returning to pre-treatment values.

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.

Metvix cream is supplied in a tube containing 1g or 2 g cream. Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Galderma International
La Défense 4 Tour Europlaza
20 Avenue André Prothin
Paris La Défense Cedex
92927
France

8 MARKETING AUTHORISATION NUMBER

PA22743/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

September 2022