METVIX 160mg/g Cream
(Methyl aminolevulinate)

Prescription Medicine For Topical Use Only

COMPOSITION

Each gram of Metvix cream contains 160mg of methyl aminolevulinate (as hydrochloride), in a vehicle base composed of self-emulsifying glyceryl monostearate, cetostearyl alcohol, polyoxyl 40 stearate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, disodium edetate, glycerol, white soft paraffin, cholesterol, isopropyl myristate, arachis oil, refined almond oil, oleyl alcohol and purified water.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics properties

Pharmacotherapeutic group:

Antineoplastic agent, ATC Code: L01X D03

Mechanism of Action

- *Metvix with red light in actinic keratoses (AK), basal cell carcinoma (BCC) and Bowen's disease*

After topical application of methyl aminolevulinate, porphyrins will accumulate intracellularly in the treated skin lesions. The intracel1ular 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. Daylight may not be sufficient for Metvix daylight treatment during winter months in certain parts of Europe. Metvix 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.

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).

Pharmacokinetic properties

In vitro dermal absorption of radio-labeled 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/cm2, complete photobleaching occurs with levels of porphyrins returning to pre-treatment values.

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.

INDICATIONS
Metvix cream is indicated for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other therapies are considered less appropriate. Metvix cream is only indicated for the treatment of superficial and/or nodular basal cell carcinoma (BCC) 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.

Metvix cream is also indicated for the 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

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients, which include arachis oil (peanut oil) and almond oil. Metvix cream is contraindicated for use in Morpheaform basal cell carcinoma and Porphyria.

INTERACTIONS
No specific interaction studies have been performed with methylaminolevulinate.

PREGNANCY AND LACTATION

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 Preclinical safety data). Metvix is not recommended during pregnancy and in women of childbearing potential not using contraception.

It is unknown whether methyl aminolevulinate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued for 48 hours after application of Metvix cream.

POSOLOGY AND METHOD OF ADMINSTRATION

POSOLOGY

Adults (including the elderly)

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 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 cream, 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

AK, BCC and Bowen's disease using red light
Apply a layer of Metvix cream (about 1 mm thick) by using a spatula to the lesion and the surrounding 5-10 mm of normal skin. Cover the treated area with an occlusive dressing for 3 hours.
Remove the dressing, and clean the area with saline and immediately expose the lesion to red light with a continuous spectrum of 570-670 nm and a total light dose of 75 J/cm^2 at the lesion surface. Red light with a narrower spectrum of approximately 630 nm (and a total light dose of 37 J/cm^2) giving the same activation of accumulated porphyrins may be used. The light intensity at the lesion surface should not exceed 200 mW/cm2.

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.

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 response 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.

AK using daylight

Metvix 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 daylight treatment should not be used.

A sunscreen should be applied, please see section “Special Warnings And Precautions For Use”. Once sunscreen has dried, scales and crusts should be removed from the lesions and the skin surface roughened before applying a thin layer of Metvix cream to the treatment areas. No occlusion is necessary. 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 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.

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. Accordingly, it should only be administered in the presence of a physician, a nurse or other health care professionals trained in the use of photodynamic therapy with Metvix.

When using Metvix with 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.

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 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.

Efficacy and safety has been investigated in studies for up to 3-6 months for actinic keratosis, up to 12 months for basal cell carcinoma and 24 months for Bowen's disease. Experience of long term efficacy is limited

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

Body system (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.

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).

OVERDOSAGE
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 light intensity.

PRESENTATION
Metvix is supplied in an aluminum tube with white cap, containing 2g cream.

STORAGE INSTRUCTION
Store at 2°C -8°C (in a refrigerator). The product must be used within three months after first opening of the container.

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