

PACKAGE INSERT

SCHEDULING STATUS:

Schedule 4

PROPRIETARY NAME (and dosage form):

METVIX[®] CREAM 160mg/g

COMPOSITION

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

Each gram of cream contains 2 mg of methyl parahydroxybenzoate and 1 mg of propyl parahydroxybenzoate as preservatives.

PHARMACOLOGICAL CLASSIFICATION:

A.26 Cytostatic Agent

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

After topical application of methyl aminolevulinate, porphyrins will 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.

Pharmacokinetics:

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 skin 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.

Pre-clinical studies on general toxicity and genotoxicity studies in the presence or absence of photoactivation, do not indicate potential risks for man. Carcinogenicity studies or studies on the reproductive function have not been performed with methyl aminolevulinate.

INDICATIONS:

METVIX 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 is only indicated 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.

CONTRA-INDICATIONS:

Hypersensitivity to the active substance or to any of the components. METVIX is contra-indicated for use in Morpheaform basal cell carcinoma and Porphyrria.

WARNINGS:

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

METVIX is not recommended during pregnancy .

There is no experience of treating pigmented or highly infiltrating lesions with METVIX cream. Thick (hyperkeratotic) actinic keratoses should not be treated with METVIX.

Efficacy and safety has been investigated in studies for up to 3 – 6 months for actinic keratoses and up to 12 months for basal cell carcinoma. Experience of long term efficacy is limited.

INTERACTIONS

No specific interaction studies have been performed with methyl aminolevulinate.

PREGNANCY AND LACTATION

For methyl aminolevulinate, no clinical data on exposed pregnancies are available. Reproductive toxicity studies in animals have not been performed. Metvix is not recommended during pregnancy.

The amount of methyl aminolevulinate excreted into human breast milk following topical administration of METVIX cream is not known. In the absence of clinical experience, breastfeeding should be discontinued for 48 hours after application of METVIX cream.

DOSAGE AND DIRECTIONS FOR USE:

Adults (including the elderly): treatment should consist of two sessions one week apart. Before applying METVIX cream, the surface of the actinic keratosis (AK) and superficial basal cell carcinoma (BCC) lesions 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.

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 lesions to red light with a continuous spectrum of 570 – 670 nm and a total light dose of 75 J/cm² at the lesion surface.

Red light with a narrower spectrum 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 minimise 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 it is recommended to confirm the response of BCC lesions by histological biopsy. At this response evaluation, lesion sites that show non-complete response may be retreated if desired.

Children and adolescents: there is no experience of treating patients below the age of 18 years.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects

Between 60 % - 80 % of patients in clinical trials experienced treatment related local phototoxicity as shown in the table below.

Skin and appendages disorders (local phototoxicity)	Very common (> 1/10)	Burning sensation, crusting, oedema, stinging skin sensation, pain, erythema
	Common (> 1/100, < 1/10)	Pruritis, ulceration, suppuration, blisters, erosion, skin infection, peeling, hyper / hypopigmentation
	Uncommon (> 1/1000<1/100)	Urticaria

There were isolated reports of anxiety, headache, dizziness, migraine, skin atrophy, abnormal lacrimation, nausea, fatigue, and influenza-like symptoms where a relationship to treatment was uncertain.

Most of the local phototoxic reactions were of mild or moderate intensity. The local phototoxicity symptoms were transient, but oedema lasted up to one week, and erythema lasted up to two weeks, but in some cases more than a year.

Repeated use did not increase the frequency or intensity of the local phototoxic reactions.

Special precautions

Sensitisation: Methyl aminolevulinate may cause sensitisation by skin contact. The excipients cetostearyl alcohol and arachis oil may rarely cause local skin reactions (e.g. contact dermatitis), methyl and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

Exposure to sunlight: Any UV therapy should be discontinued before treatment. As a general precaution, sun exposure on the treated lesion sites and surrounding skin has to be avoided for a couple of days following treatment.

Eye contact: Direct eye contact with METVIX cream should be avoided.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

A cream to pale yellow coloured cream, easily spread.

PRESENTATION:

White aluminum tubes with a white cap, containing 2g of cream

STORAGE INSTRUCTIONS:

Store at 2°C – 8°C (in a refrigerator).

The product must be used within one week after opening.

REGISTRATION NUMBER:

A/26/380528

NAME AND BUSINESS ADDRESS OF APPLICANT:

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