New Zealand Datasheet

Name of Medicine

METVIX™
Methyl aminolevulinate (as hydrochloride)

Presentation

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

Uses

Actions

Antineoplastic agent, ATC Code: L01X D03

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.

METVIX in combination with light activation is referred to as METVIX-Photodynamic Therapy (METVIX-PDT").

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 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.

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.

Dosage and Administration

Adults (including the elderly)

Before applying METVIX cream, the surface of 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 1mm thick) by using a spatula to the lesion and the surrounding 5-10mm 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/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.

BCC lesions should undergo two consecutive treatments one week apart.

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients. Morpheaform basal cell carcinoma, invasive squamous cell carcinoma of the skin, porphyria.

Warnings and Precautions

Direct eye contact should be avoided.

Methyl aminolevulinate may cause sensitization by skin contact resulting in application site eczema or allergic contact dermatitis.

The excipients cetostearyl alcohol and arachis oil (peanut oil) may rarely cause local skin reactions (e.g. contact dermatitis), methyl- and propylhydroxybenzoate (E218, E216) may cause allergic reactions (possibly delayed).

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.

METVIX 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.
Minimum effective dose is not defined.

<u>Actinic keratosis</u>
There are no data on recurrence.

There is no histological confirmation on clearance of lesions.

There are no data on patients previously treated with 5FU or tretinoin.

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

Basal cell carcinoma
The efficacy of METVIX in treating basal cell carcinomas that have recurred following previous treatment has not been determined. Therefore, METVIX should only be used in the treatment of primary lesions.

There is no experience in treating basal cell carcinomas associated with xeroderma pigmentosum, Gorlin's syndrome or immunosuppressive therapy.

The sites of successfully treated lesions should be reviewed at 6-12 monthly intervals to detect recurrence.

Use in Pregnancy
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.

Use in Lactation
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.

Effects on Ability to Drive and Use Machines
Not applicable.

Use in Children
There is no experience of treating patients below the age of 18 years. METVIX is not recommended for use in children.

Use in the Elderly
No dosage adjustment required.

Impaired Renal or Hepatic Function
No information is available on the use of METVIX in this population.

Carcinogenicity, Mutagenicity and Impairment of Fertility
Studies on the carcinogenic potential of methyl aminolevulinate have not been performed.

There was no consistent evidence for genotoxic activity of methyl aminolevulinate and its metabolites in an in vitro assay of gene mutation or a chromosomal damage assay in vitro in the presence or absence of photoactivation, or in a chromosomal damage assay in-vivo in the absence of photoactivation.

Studies on the reproductive toxicity of methyl aminolevulinate have not been performed.

Adverse Effects
Between 60 % and 80% of patients in clinical trials experienced reactions localised to the treatment site that are attributable to the toxic effects of the photodynamic therapy (phototoxicity) or to the 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 resolution on the day of treatment. The severity is usually mild or moderate, but rarely, it may require early termination of illumination. The most frequent signs of phototoxicity are erythema and

oedema which may persist for 1 to 2 weeks or occasionally for longer. In two cases they persisted for more than one year.

Incidence of Local Adverse Reactions – Clinical Trials

Skin and appendage disorders	Very common (>1/10)	Pain and discomfort described as pain, burning, warm, stinging, pricking and tingling skin, erythema, itching, oedema
	Common (>1/100, < 1/10)	Crusting, ulceration, blisters, suppuration, infection peeling, application site reactions, bleeding skin, hypo/hyperpigmentation
	Uncommon (>1/1000 <1/100)	Rash, urticaria, eczema

Uncommon (<1%) non-local adverse events are headache, nausea, eye pain, eye irritation, fatigue and dizziness. There were isolated reports of scar where a relationship to treatment was uncertain.

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

Adverse Reactions – Post Marketing
Application site eczema and allergic contact dermatitis have been described in post-marketing reports. Most cases were localised to the treatment area and were not severe. Erythema and swelling have been more extensive on rare occasions

Interactions

No specific interaction studies have been performed with methyl aminolevulinate.

Overdosage

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.

Further Information

Excipients

Self-emulsifying glyceryl monostearate, cetostearyl alcohol, poloxyl 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.

Clinical Trials

Actinic keratosis (AK)
The clinical trial programme to establish the efficacy and safety of METVIX for the treatment of AK comprises a total of 831 patients who participated in controlled studies of which 568 patients with 1829 lesions were treated with METVIX. A further 423 patients with 1470 AK lesions were treated in the compassionate-use programme.

Controlled studies included the two pivotal placebo-controlled studies of METVIX-PDT for the treatment of lesions on the face and scalp (see results presented below), one placebo-controlled study (PC T302/99) and one active-controlled study of METVIX-PDT versus cryotherapy (PC T301/99), both of which involved treatment of AK lesions at any site on the body.

Two randomized, double-blind placebo-controlled studies have been conducted in Australia and USA. Patients who were included had previously untreated facial and scalp actinic keratoses (AKs) that were slightly palpable (better felt than seen) to moderately thick (easily felt and seen). Hyperkeratotic actinic keratosis lesions were

excluded. METVIX 160 mg/g cream or placebo cream was applied for 3 hours before illumination with a light dose of 75 J/cm^2 (wavelength 570 to 670 nm). Two treatment sessions were given 7 days apart. A “cleared” AK lesion was defined as being not visible and not palpable when assessed 3 months after the second treatment session. Patients with all treated lesions cleared at 3 months were defined as Complete Responders. The percentage of patients in whom 100% of the lesions were cleared is shown below:

	Australian Study (PC T305/99) ITT population		U.S. Study (PC T306/99) ITT population	
	METVIX-PDT	Placebo-PDT	METVIX-PDT	Placebo-PDT
Number of patients	88	23	42	38
Number of lesions treated	360	74	260	242
Patients with Complete Response	71/88 (81%) 95 CI: 70.9%-88.3%	3/23 (13%) 95 CI: 2.8-33.6%	33/42 (79%) 95 CI: 63.2%-89.7%	8/38 (21%) 95 CI: 9.6%-37.3%

The Australian study PC T305/99 included a third arm consisting of treatment with one freeze thaw cycle with liquid nitrogen spray. The results of the PP population are presented below:

	Australian Study (PC T305/99) PP population	
	METVIX-PDT	Cryotherapy
Number of patients	77	86
Number of lesions treated	295	407
Clinic Patients with Complete Response	63/77 (81.8%) 95 CI: 71.4%-89.7%	51/86 (59.3%) 95 CI: 42.2%-69.8%

An open, non-inferiority, randomized study, PC T311 was conducted in Sweden to compare two treatment regimens of METVIX-PDT in patients with up to 10 clinically confirmed mild to moderate AK lesions on the face or scalp. A total of 211 patients with 413 lesions were included in the study. METVIX 160 mg/g cream was applied for 3 hours before illumination with an LED light source with an average wavelength of 630 nm and a light dosage of 37J/cm^2.

Regimen I: Patients were treated once with METVIX-PDT. Lesions with non-complete response were given one further treatment at the 3-month-visit.

Regimen II: Treatment with METVIX-PDT consisted of two treatment sessions one week apart.

All patients were clinically assessed three months after their final METVIX treatment. Patient complete response rates (i.e. the proportion of patients where all lesions had shown a complete clinical response) and lesion complete response rates for each treatment group in the PP population were as follows:

	METVIX regimen I	METVIX regimen II	Total
No. patients treated	105	106	211
Patient Complete Response Rate	89 %	80 %	
Lesion Complete Response	92 %	87 %	

The efficacy of a single initial treatment of METVIX PDT was not inferior to two treatments administered 7 days apart when the difference between regimen I and regimen II was calculated to be less than 15% (one sided, upper limit, CI 97.5%)

Superficial and/or nodular basal cell carcinoma (BCC)
The clinical trial program to establish the efficacy and safety of METVIX for the treatment of superficial and/or nodular BCC comprised a total of 480 patients, of which 341 patients with 498 lesions were treated with METVIX-PDT.

The American pivotal double-blind placebo-controlled study PC T307/00 showed that PDT with METVIX is superior to PDT with placebo cream in nodular BCC. Active controlled studies included the European studies PC T303/99 which compared METVIX-PDT to surgery in nodular BCC and PC T304/99 which compared METVIX-PDT to cryotherapy in superficial BCC. The superficial lesions were initially treated with one PDT session, whereas nodular lesions were given two PDT sessions one week apart. The results of these studies are presented below.

	American Study (PC T307/00) ITT population	
	METVIX-PDT	Placebo-PDT
Number of patients	33	32
Number of lesions treated	41	39
Patients with histologically verified Complete Response 6 months post-treatment	25/33 (76%) 95 CI: 58%-89%	11/32 (34%) 95 CI: 19%-53%

	European Study (PC T303/99) PP population		European Study (PC T304/99) PP population	
	METVIX-PDT	Surgery	METVIX-PDT	Cryotherapy
Number of patients	50	47	58	57
Number of lesions treated	53	52	102	98
Patients with Complete Response 6 months post-treatment	45/50 (90%) 95 CI: 78%-97%	46/47 (98%) 95 CI: 89%-100%	55/58 (95%) 95 CI: 86%-99%	52/57 (91%) 95 CI: 81%-97%

Lesion recurrence was assessed at 24 months for all lesions that were disease-free 3 and 12 months after the last treatment. The lesion recurrence rates at 24 months are given below:

	European Study (PC T303/99)		European Study (PC T304/99)	
Study status	METVIX-PDT	Surgery	METVIX-PDT	Cryotherapy
Non-recurrence	31/48 (65%)	43/51 (84%)	82/108 (76%)	70/94 (74%)
Recurrence	3/48 (6%)	1/51 (2%)	18/108 (17%)	19/94 (20%)
Missing	14/48 (29%)	7/51 (14%)	8/108 (7%)	5/94 (5%)

Long term outcomes beyond 24 months are unknown.

Incompatibilities
Not applicable.

Medicine Classification
Prescription Medicine.

Pharmaceutical Precautions

Store at below 8ºC (in a refrigerator)

Keep out of reach of children.

Discard 1 week after opening tube.

Package quantities

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

Name and Address

Galderma Australia Pty Ltd
Suite 4, 13b Narabang Way
Belrose NSW
Australia 2085

Distributed in New Zealand by
Healthcare Logistics

58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph (09) 918 5100
Fax (09) 918 5101

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