

New Zealand Datasheet

1 PRODUCT NAME

METVIX™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methyl aminolevulinate (as hydrochloride) 16%

3 PHARMACEUTICAL FORM

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

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.

Metvix is indicated in adults above 18 years of age.

4.2 Dosage and method of administration

Adults (including the elderly)

For treatment of actinic keratoses (AK), one session of photodynamic therapy (PDT) should be administered with either red LED light via a suitable lamp (c-PDT) or exposure to natural daylight (DL-PDT). Treated lesions should be assessed after three months and those with non-complete response should be retreated, as per the initial treatment method.

For treatment of basal cell carcinoma (BCC) two sessions of c-PDT should be administered with an interval of one week between sessions.

Treated lesions should be assessed after three months and those with non-complete response should be retreated, as per the initial treatment method. In clinical trials in BCC, approximately 25-30% of patients required retreatment at 3 months.

Procedure for AK and BCC using red LED light

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 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/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.

Close long term clinical monitoring of BCC is recommended, with histology if necessary.

Procedure for AK using daylight

If deemed appropriate, patients with AK may be treated with METVIX activated by daylight (DL-PDT), instead of using red LED light (c-PDT). METVIX DL-PDT treatment is exclusively for patients with face and scalp AK, and results in significantly lower pain scores than with c-PDT treatment.

METVIX DL-PDT treatment can be used if the weather is 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. An appropriate sunscreen should be applied to all exposed areas. The sunscreen used must offer adequate protection (SPF 30 or higher) and 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 procedure.

Sunscreen should be applied 15 minutes prior to lesion preparation. The surface and surrounding area of the AK lesions should be prepared by removing scales and crusts and roughening the surface of the lesions. METVIX cream should then be applied however no occlusion is necessary.

Daylight exposure should begin within 30 minutes and continue for 2 hours. During this time, patients should remain outside, and carry out usual daily activities. 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 cream should be removed with saline water.

Treated lesions should be evaluated after 3 months and, if necessary, a second treatment session should be repeated.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Methyl aminolevulinate may cause sensitization by skin contact resulting in angioedema,

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.

In patients with a history of hypertension, pain during illumination may induce increased blood pressure. It is thus recommended to measure blood pressure in these patients who experience severe pain, and interrupt illumination (in addition to taking specific measures when needed) if these patients also present severe hypertension.

METVIX with red LED light 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.

Actinic keratosis

There is no histological confirmation on clearance of lesions nor 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.

Impaired renal or hepatic function

No information is available on the use of METVIX in this population.

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.

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been performed with methyl aminolevulinate.

4.6 Fertility, Pregnancy and lactation

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

Use in Pregnancy

(Category B2)

No clinical data on exposed pregnancies are available for methyl aminolevulinate. No reproductive studies in animals have been performed. The potential risk is unknown. Methyl aminolevulinate is not recommended during pregnancy.

Use in Lactation

There are no human data on the excretion of methyl aminolevulinate in human breast milk or on the safety of methyl aminolevulinate exposure in newborns/infants following topical application of METVIX. A risk to the newborns/infants cannot be excluded. Therefore, breastfeeding should be discontinued for 48 hours after application of METVIX cream.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Between 60 % and 80% of patients in clinical trials using conventional Photodynamic Therapy (c-PDT) 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 (c-PDT)

Skin and subcutaneous tissue disorders	Very common (>1/10)	Pain and discomfort described as pain, burning, warm, stinging, pricking and tingling skin, erythema, itching, face 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 pastular, urticaria, application site eczema, skin irritation.

The following non-local adverse events were reported in clinical trials (c-PDT):

Nervous system disorders

Uncommon: headache, dizziness

Eye disorders

Uncommon: Eye pain, eye irritation, eye swelling

Vascular disorders:

Uncommon: Wound haemorrhage

Gastrointestinal disorders

Uncommon: Nausea

General disorders and administration site conditions

Uncommon: Fatigue

There were also 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.

In the Australian study comparing DL-PDT to c-PDT, 39% of patients treated with daylight (versus 59% for patients treated with c-PDT) reported at least one treatment-related adverse effect, the most frequent ($\geq 4.0\%$) being skin reaction, scab, photosensitivity reaction and skin pain.

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. Eyelid oedema, face oedema (swelling face), rash pustular, angioedema and hypertension have also been described in post-marketing reports.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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

For information on the management of overdose, contact the Poison Information Centre on 0800 746766

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antineoplastic agent, ATC Code: L01X D03

After topical application of methyl aminolevulinate, during the 3 hours under occlusion, 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™).

When methyl aminolevulinate is used with natural daylight, the procedure consists of continuous light exposure. PpIX is continuously being produced and activated within the target cells creating a constant micro-phototoxic effect without the PpIX accumulation associated with conventional-Photodynamic Therapy (c-PDT).

Clinical Trials

Actinic keratosis (AK)

Treatment with red LED light

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/cm² (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/cm².

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%).

Another study with conventional photodynamic therapy (c-PDT) showed that over 50% of patients with a complete response after 3 months had no recurrence after 1 year follow-up.

Treatment with Daylight

The efficacy and safety of Metvix daylight photodynamic therapy (DL-PDT) was compared to METVIX conventional photodynamic therapy (c-PDT) in a 24-week randomised, investigator-blinded, intra-individual study conducted across 7 Australian centres. One hundred patients aged over 18 years with mild AK and with or without moderate AK were treated on one side of the face or scalp with METVIX DL-PDT and on the contralateral side with METVIX c-PDT. The c-PDT treatment procedure consisted of gentle curettage of lesions, then METVIX cream application, followed by area occlusion, then dressing removal, and finally 7-10 minutes photodynamic treatment with red LED light via a suitable lamp. The DL-PDT procedure consisted of gentle curettage of lesions, Metvix application without occlusion and, after 30 minutes, a 2h exposure to daylight.

Both the efficacy and safety of METVIX DL-PDT were addressed with two co-primary endpoints. The co-primary efficacy endpoint was the percentage change from baseline in the total number of treated mild lesions per side at Week 12 (non-inferiority of METVIX DL-PDT compared to METVIX c-PDT). The co-primary safety endpoint was subject assessment of maximal pain per side at the Baseline treatment session (superiority of METVIX DL-PDT compared to METVIX c-PDT).

The study results demonstrated that DL-PDT is as effective as c-PDT for treating AK lesions (percentage change from baseline in the total number of treated mild lesions per side after 12 weeks), but with significantly reduced subject pain. METVIX DL-PDT treatment benefit was similar (non-inferior) to METVIX c-PDT (89.2% vs 92.8%, per protocol population) at week 12 after one session and the maintenance of lesion response rate remained non-inferior for patients presenting at week 24 (96% for DL-PDT and 96.6% for c-PDT).

All subjects received an effective light dose on the DL-PDT treated side (22.8 ± 12.4 J/cm²). No correlation was found between light dose received by subjects and efficacy or safety variables.

The safety results of this AK study with DL-PDT compared to c-PDT showed that both treatment arms were well tolerated. Pain was assessed on an 11-point scale ranging from 0 (no pain at all) to 10 (extreme pain). DL-PDT was associated with significantly less pain compared to c-PDT (0.8 vs 5.7, $p < 0.001$); 81.6% subjects reported no pain with DL-PDT vs 2% with c-PDT (see Adverse Effects).

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:

Study status	European Study (PC T303/99)		European Study (PC T304/99)	
	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.

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. With conventional PDT, 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.

5.3 Preclinical safety data

Carcinogenicity

Studies on the carcinogenic potential of methyl aminolevulinate have not been performed.

Genotoxicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of 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 (peanut oil), refined almond oil, oleyl alcohol and purified water.

6.2 Incompatibilities

METVIX should not be mixed with other drugs or preparations

6.3 Shelf life

15 months.

6.4 Special precautions for storage

Store at below 8°C (in a refrigerator) Keep out of reach of children.

Discard 28 days after opening tube.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

Not applicable.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Sponsor and distributor in New Zealand

Healthcare Logistics

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Airport Oaks

Auckland

New Zealand

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Fax (09) 918 5101

For:

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9 DATE OF FIRST APPROVAL

7 February 2002

10 DATE OF REVISION OF THE TEXT

3 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.4	In-use shelf life changed from 1 week to 28 days