

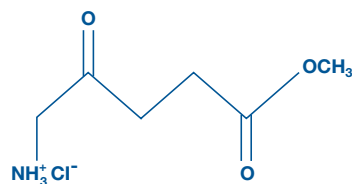
# PRODUCT INFORMATION

## Metvix® 160mg/g Cream

**NAME OF THE DRUG: Methyl aminolevulinate (as hydrochloride).**

### DESCRIPTION

#### Structural formula:



Metvix® cream contains 160 mg/g of methyl aminolevulinate (as hydrochloride) and is cream to pale brown in colour. Other excipients are glyceryl monostearate (self emulsifying), cetostearyl alcohol, PEG-40 stearate, methyl hydroxybenzoate, propyl hydroxybenzoate, disodium edetate, glycerol, white soft paraffin, cholesterol, isopropyl myristate, arachis oil (peanut oil), almond oil (refined), oleyl alcohol and purified water.

**CAS number: 79416-27-6**

### PHARMACOLOGY

Methyl aminolevulinate is an antineoplastic agent. 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.

In humans, the selective accumulation of porphyrins in lesions compared to normal skin has been demonstrated with Metvix®. 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<sup>2</sup>, or an LED light source with an average wavelength of 630 nm and a light dosage of 37J/cm<sup>2</sup>, complete photobleaching occurs with levels of porphyrins returning to pre-treatment values.

### 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<sup>2</sup> (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 are 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
<b>Number of patients</b>	88	23	42	38
<b>Number of lesions treated</b>	360	74	260	242
<b>Patients with Complete Response</b>	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
<b>Number of patients</b>	77	86
<b>Number of lesions treated</b>	295	407
<b>Clinic Patients with Complete Response</b>	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%).

### 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.

### Squamous cell carcinoma in situ (Bowen's disease)

A clinical trial to establish the efficacy and safety of Metvix® for the treatment of squamous cell carcinoma *in situ* (Bowen's disease) comprised a total of 225 patients, 96 of whom were treated with Metvix® PDT. This study, PC T309/00, was a prospective, randomised placebo-controlled multicentre European study in which patients were treated with either Metvix® PDT; placebo PDT; cryotherapy or 5-fluorouracil 5% cream (5-FU). Randomisation was to either PDT or standard therapy. Standard therapy was either cryotherapy or fluorouracil at the physician's choice. Within the PDT group, patients were further randomized in the ratio 5: 1 to either Metvix® PDT or placebo PDT. The comparison with placebo-PDT was double-blinded; however, the comparison with the other treatments was unblinded. Responses to treatment were based on clinical, not histological, assessment.

There were 275 lesions in the 225 patients. The distribution of lesions was similar in all groups: 65% of lesions were located on the extremities, 23% on the face and scalp and 12 % on the neck or trunk. Patients with large lesions (>40mm in diameter), strongly pigmented lesions or genital lesions were excluded.

Metvix® cream was applied 3 hours prior to illumination in two sessions one week apart. Light dose was 75J/cm<sup>2</sup> (wavelength 570-670 nm). Partial responders received a second cycle of treatment 3 months later. Metvix® PDT (n=96) was significantly superior to placebo-PDT (n=17) in complete response rate at 3 months after one cycle – 73% vs 24%, p< 0.001 - in the intent-to-treat analysis.

Metvix® PDT was non inferior to cryotherapy and fluorouracil in complete response rate 3 months after 1-2 cycles of treatment based on the upper-bound of the 97.5 % confidence interval of the difference being less than 15% (table).

<b>METVIX® PDT in Bowen's Disease: comparison with Cryotherapy and 5-FU</b>			
<b>Parameter</b>	<b>Metvix-PDT n=96</b>	<b>Cryotherapy n=82</b>	<b>5-FU n=30</b>
CR 3 months (PP)	91% (n=91)	88% (n=77)	81% (n=26)
97.5% CI <sub>μ</sub> of difference		4.4%	7.4%
95% CI of difference		(-12.1%, 6.3%)	(-26.7, 5.8%)
CR-3 months (ITT)	86%	84%	80%
97.5% CI <sub>μ</sub> of difference		8.3%	12.4%
95 % CI of difference		(-12.8%, 8.1%)	(-22.3%, 9.4%)
CR-24 months (ITT)	60%	56%	53%
95 % CI of difference		(-18.8%, 10.2%)	(-27.4%, 13.3%)
Recurrence – 24 months (patients with CR)	22% (n=83)	26% (n=69)	25% (n=24)

CR-Patient Complete Response i.e. complete disappearance of the lesion (s). Lesion response rates were similar to patient response rates. 5-FU-Fluorouracil. PP- Per Protocol. ITT- Intent-to-Treat. Cryotherapy - Metvix® PDT and 5-FU-Metvix® PDT.

### INDICATIONS

Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable. Primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate. Treatment of biopsy-proven squamous cell carcinoma *in situ* (Bowen's disease), where surgery is considered inappropriate.

### CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients including arachis oil (peanut oil).  
Morpheaform basal cell carcinoma.  
Invasive squamous cell carcinoma of the skin.  
Porphyria.

### PRECAUTIONS

#### General

Direct eye contact should be avoided.

Methyl aminolevulinate may cause sensitization by skin contact. The excipients cetostearyl alcohol and arachis 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.

#### Actinic keratosis

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.

### **Squamous cell carcinoma in situ (Bowen's disease)**

There is no experience of treating lesions which are pigmented, highly infiltrating or located on the genitalia with Metvix® cream. There is no experience of treating Bowen's disease lesions larger than 40 mm in diameter.

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

The efficacy of Metvix® in treating Bowen's disease lesions that have recurred following previous treatment has not been determined. Therefore, Metvix® should only be used in the treatment of primary lesions.

### **Interaction with other drugs**

No specific interaction studies have been performed with Metvix®.

### **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 elderly**

No dosage adjustment required.

### **Impaired renal or hepatic function**

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

### **Carcinogenesis and mutagenesis**

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.

### **Impairment of Fertility**

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 infants following topical application of Metvix®. Therefore, breastfeeding should be discontinued for 48 h after application of Metvix®.

### **Effects on ability to drive and use machines**

No effects on ability to drive and use machines have been observed.

## **ADVERSE REACTIONS**

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 skin sensations. The severity is usually mild or moderate, but rarely, it may require early termination of illumination. Typically phototoxicity is experienced at the time of illumination or soon after and lasts for a few hours, generally resolving on the day of treatment. Other 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.

<b>Incidence of Local Adverse Reactions</b>		
<b>Skin and appendages disorders</b>	<b>Very common (&gt;1/10)</b>	Pain and discomfort described as pain, burning, warm, stinging, pricking and tingling skin, erythema, itching, oedema
	<b>Common (&gt;1/100, &lt;1/10)</b>	Crusting, ulceration, blisters, suppuration, infection, peeling, application site reactions, bleeding skin, hypo/hyperpigmentation
	<b>Uncommon (&gt;1/1000 &lt;1/100)</b>	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.

## **DOSAGE AND ADMINISTRATION**

### **Adults (including the elderly)**

For treatment of actinic keratoses (AK) one session of photodynamic therapy should be administered.

For treatment of basal cell carcinoma (BCC) and squamous cell carcinoma *in situ* (Bowen's disease) two sessions 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. In the clinical trial in Bowen's disease, approximately 20% of patients required retreatment at 3 months.

Before applying Metvix®, the surface of the lesions should be prepared by removing scales and crusts and roughening the surface of the lesion. 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® (about 1 mm thick, 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, 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<sup>2</sup>, or an LED light source with an average wavelength of 630 nm and a light dosage of 37J/cm<sup>2</sup>, giving the same activation of accumulated porphyrins may be used at the lesion surface. The light intensity at the lesion surface should not exceed 200 mW/cm<sup>2</sup>.

Only lamps listed in the Australian Register of Therapeutic Goods 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.

### ***Instruction for use / handling***

Metvix® should not be mixed with other drugs or preparations

### ***Storage***

Shelf life of unopened container: 12 months.

1 week after first opening of the container.

Store below 8 degrees Celsius. Refrigerate.

## **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.

## **PRESENTATION**

Metvix® is supplied in tubes containing 2 g cream

## **POISON SCHEDULES** S4

**SPONSOR** Galderma Australia Pty Ltd

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AUSTR.No: 93838

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