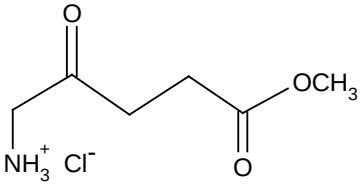
PRODUCT INFORMATION
METVIX®

NAME OF THE MEDICINE
Methyl aminolevulinate (as hydrochloride).
Structural formula:



CAS number: 79416-27-6

DESCRIPTION
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.

PHARMACOLOGY
Methyl aminolevulinate is an antineoplastic agent. After topical application of methyl aminolevulinate, during the 3 hours under occlusion, porphyrins will accumulate intracellulary 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).

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. 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/cm^2, or an LED light source with an average wavelength of 630 nm and a light dosage of 37J/cm^2, complete photobleaching occurs with levels of porphyrins returning to pre-treatment values.

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/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 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
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
ClinicPatients 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%)

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/cm^2). 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 section).

<u>Superficial and/or nodular basal cell carcinoma (BCC)</u>
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.

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 fluorouacil 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^2 (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).

METVIX –PDT in Bowen's Disease: comparison with Cryotherapy and 5-FU

Parameter	Metvix-PDT n=96	Cryotherapy n=82	5-FU n=30
CR 3 months (PP)	91% (n=91)	88% (n=77)	81% (n=26)
97.5% CI of difference		4.4%	7.4%
95 % CI of diff		(-12.1%, 6.3%)	(-26.7, 5.8%)
CR-3 months (ITT)	86 %	84 %	80 %
97.5% CI of difference		8.3%	12.4%
95 % CI of diff		(-12.8%, 8.1%)	(-22.3%, 9.4%)
CR-24months (ITT)	60 %	56 %	53 %
95 % CI of diff		(-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.

Metvix is indicated in adults above 18 years of age.

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. 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 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.

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.

Impaired renal or hepatic function
No information is available on the use of Metvix in this population.

Effects on 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 newborns/infants following topical application of Metvix. A risk to the newborns/infants cannot be excluded. Therefore, breastfeeding should be discontinued for 48 h after application of Metvix.

Paediatric Use
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.

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.

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

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

INTERACTIONS WITH OTHER MEDICINES
No specific interaction studies have been performed with Metvix.

ADVERSE 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.

Table: 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 pustular, urticaria, application site eczema, skin irritation

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

<u>Nervous system disorders</u>
Uncommon: headache, dizziness

<u>Eye disorders</u>
Uncommon: Eye pain, eye irritation, eye swelling

Vascular disorders:
Uncommon: Wound hemorrhage

<u>Gastrointestinal disorders</u>
Uncommon: Nausea

<u>General disorders and administration site conditions</u>
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 (≥ 4.0%) being skin reaction, scab, photosensitivity reaction and skin pain.

Adverse Reactions – Post Marketing (c-PDT)
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.

DOSAGE AND 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) and squamous cell carcinoma *in situ* (Bowen's disease) 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. In the clinical trial in Bowen's disease, approximately 20% of patients required retreatment at 3 months.

Procedure for AK, BCC and Bowen's disease using red LED light
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, 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, or an LED light source with an average wavelength of 630 nm and a light dosage of 37J/cm^2, 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^2.

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.

Close long term clinical monitoring of BCC and Bowen´s disease is recommended, with histology if necessary.

<u>Procedure for AK using daylight</u>
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 (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 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.

Instruction for use / handling
Metvix should not be mixed with other drugs or preparations

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 red LED light intensity.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Metvix® is supplied in tubes containing 2 g cream

Shelf life of unopened container: 15 months.
Shelf life of opened container: 28 days after first opening.
Store below 8ºC. Refrigerate.

POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

NAME AND ADDRESS OF THE SPONSOR

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

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 5 July 2003

DATE OF MOST RECENT AMENDMENT: 07 February 2019.