PRODUCT MONOGRAPH

PrMETVIX®

methyl aminolevulinate
(as methyl aminolevulinate hydrochloride)

168 mg/g

Topical cream

Anti-neoplastic Agent

Galderma Canada Inc.
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4th Floor
Thornhill, Ontario
L3T 7V9

Date of Revision: Sep. 09, 2022

Submission Control No: 180975

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Cream/ 168 mg/g methyl aminolevulinate (as methyl aminolevulinate hydrochloride)	Arachis (peanut) oil, refined almond oil *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

METVIX® cream in combination with 630 nm wavelength red light illumination using the Aktilite CL 128 lamp (conventional photodynamic therapy [c-PDT]) is indicated for the:

- treatment of thin or non-hyperkeratotic and non-pigmented actinic keratosis on the face and scalp when other therapies are considered less appropriate.
- treatment of primary superficial basal cell carcinoma outside the H-zone of the face (e.g. ears, nose) when other therapies are considered less appropriate. The lesions should have been confirmed previously by biopsy.

METVIX cream in combination with daylight (daylight photodynamic therapy [DL-PDT]) is indicated for the:

- treatment of thin or non-hyperkeratotic and non-pigmented actinic keratosis on the face and scalp when other therapies are considered less appropriate.

METVIX should be administered in the physician's office by a trained healthcare professional only. Care should be taken when applying METVIX cream to avoid inadvertent skin contact (see Warnings and Precautions). This product is not intended for application by patients or unqualified medical personnel; therefore, this product is only dispensed to physicians.

Geriatrics (> *65* years of age): No overall differences in safety and efficacy were observed between patients aged 65 years and older and those who were younger.

Pediatrics: It is not recommended that METVIX cream be used in pediatric patients (see Warnings and Precautions).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or aminolevulinic acid or to any ingredient in the formulation (including peanut and almond oil) or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with cutaneous photosensitivity/porphyria, or known allergies to porphyrins.
- Patients with morpheaform basal cell carcinoma.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- METVIX cream is intended for topical use. Do not apply to the eyes or to mucous membranes.
- METVIX should be administered by trained healthcare professionals only.
- Care should be taken when applying METVIX cream to avoid inadvertent skin contact (see Sensitivity/Resistance section below).
- Patients with sBCC treated with METVIX c-PDT must have regular follow-up of the treatment site since the efficacy is generally less than with surgery.
- The long-term efficacy of METVIX c-PDT for the treatment of sBCC has not been established. Data from studies performed with a different lamp showed that the sBCC lesion complete response (CR) at 12 months was similar to that observed with the Aktilite CL128 lamp, but decreased to 29-60% at 60 months post-treatment.

General

Any UV-therapy should be discontinued before treatment. Direct eye contact with METVIX cream should be avoided.

METVIX c-PDT: During the time period between the application of METVIX cream and exposure to red light illumination, the treatment site will become photosensitive. After METVIX cream application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to red light treatment. Exposure to light may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat, protective clothing, or similar covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. The treated site should be protected from

extreme cold with adequate clothing or remaining indoors between application of METVIX cream and photodynamic therapy light treatment.

After illumination of METVIX cream, the area treated should be kept covered and away from light for at least 48 hours.

Because of the potential for skin to become photosensitized, METVIX cream should be applied by a trained physician to the skin lesion and perilesional skin within 5 mm of the lesion. Redness, swelling, burning and stinging are expected as a result of therapy; however, if these symptoms increase in severity and persist longer than 3 weeks, the patient should contact their doctor.

Photosensitivity and Device Precautions – METVIX c-PDT: The patient, operator and other persons present during red light treatment should wear protective goggles that sufficiently screen out red light with wavelengths from 570 to 670 nm. METVIX cream used with red light is not intended for use with any device other than the approved lamp: Aktilite CL.

If for any reason the patient cannot have the red light treatment after application of METVIX cream, the cream should be rinsed off, and the patient should protect the treated area from sunlight, prolonged or intense light for two days. Prolonged exposure for greater than 4 hours to METVIX cream should be avoided.

METVIX DL-PDT: METVIX DL-PDT can be used if the temperature conditions (ideally >10°C and <35°C) are suitable to stay comfortably outdoors for 2 hours. Daylight conditions may not be sufficient for METVIX DL-PDT from November to March. If the weather is rainy, snowy or likely to become so, METVIX DL-PDT should not be used.

If daylight exposure cannot be performed as planned, the METVIX cream should be rinsed off. The patient should protect the treated area from sunlight, prolonged or intense light for two days.

Carcinogenesis and Mutagenesis

Please see Toxicology section. Long-term studies to evaluate the carcinogenic potential of METVIX cream have not been performed.

Cardiovascular

Pain during illumination may induce increased blood pressure. Acute post-procedure hypertension and hypertensive crisis associated with pain during METVIX PDT have been reported. Severe hypertension was more frequently reported in patients with baseline hypertension, with severe pain or treated with large lesion area on the head. It is recommended to measure blood pressure in patients who experience severe pain. Illumination should be interrupted (in addition to taking specific measures when needed) if these patients also present severe hypertension.

Hematologic

METVIX cream has not been tested on patients with inherited or acquired coagulation defects.

Hepatic/Biliary/Pancreatic
The results of repeated-dose toxicity studies indicated that the liver was the target organ for high intravenous doses of methyl aminolevulinate in rats, but examination of liver function tests from phase I trials in humans did not reveal any changes that were inconsistent with random variation.

Immune
A study conducted in immunocompromised organ transplant recipients did not identify any safety concern in this population, adverse events being similar to those reported in trials in immunocompetent patients. However, the efficacy of METVIX in immunocompromised patients has not been well established.

Ophthalmologic
Application of METVIX cream to the eyes or to mucous membranes should be avoided.

Sensitivity/Resistance
Methyl aminolevulinate may cause sensitization by skin contact resulting in application site eczema or allergic contact dermatitis or more severe reactions such as angioedema. The excipients cetostearyl alcohol and peanut oil may elicit local skin reactions such as contact eczema in rare cases, while methylparaben and propylparaben may sometimes cause allergic reactions.

Contact sensitization (allergenicity) has been observed in 14-52% of subjects previously exposed to METVIX on at least 4 occasions (See Toxicology/Special Tolerance Studies in Humans). Cases of angioedema, eyelid edema, and face edema have been reported in the post-market setting. METVIX treatment should be discontinued in patients who experienced severe hypersensitivity reactions.

Care should be taken by the physician when applying METVIX cream to avoid inadvertent skin contact. Nitrile gloves should be worn when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection when using this product.

Sexual Function/Reproduction
The effect of METVIX PDT on sexual function and reproduction has not been investigated.

Skin
The safety and efficacy of METVIX cream has not been established in patients with porphyria or pigmented or highly infiltrating lesions. Thick (hyperkeratotic) actinic keratosis should not be treated with METVIX cream.

Please see "General" above for precautions regarding photosensitivity reactions.

Special Populations
Pregnant Women: Intravenous methyl aminolevulinate was teratogenic in rabbits at a high dose (see Toxicology). It is not known whether METVIX cream can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Treatment with METVIX cream is not recommended during pregnancy. METVIX cream should be given to pregnant women only if the benefit risk ratio is favourable.

Nursing Women: The amount of methyl aminolevulinate secreted into human breast milk following topical administration of METVIX cream is not known. In the absence of clinical studies and because many drugs are excreted in human milk, a risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued for 48 hours after application of METVIX.

Pediatrics: Actinic keratosis and basal cell carcinoma are seldom observed under the age of 18 and therefore, there is no experience with the use of METVIX-PDT in this population.

METVIX cream is not recommended for use in pediatric patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions are categorized as appearing at the treatment site or non-treatment site. The common adverse drug reactions reported in all studies of METVIX-PDT were local phototoxic reactions. Phototoxic reactions corresponded to reactions localized to the treatment site that are attributable to toxic effects of the photodynamic therapy. The most frequent symptoms are painful and burning skin sensation, typically beginning during illumination or soon after, lasting for a few hours and resolving on the day of treatment. The most frequent signs of phototoxicity are erythema and scab. The majority are of mild or moderate severity, rarely require early termination of illumination when using a lamp, and persist for 1 to 2 weeks or occasionally longer.

Clinical Trial Adverse Drug Reactions

Actinic Keratosis Studies Using METVIX c-PDT:
A total of 231 subjects, each with 4 - 10 actinic keratoses were enrolled in 2 double-blind, randomized, vehicle-controlled clinical trials (Studies PC T404/05 and PC T405/05). Subjects were randomized to receive Aktilite PDT with METVIX cream or vehicle cream on 2 occasions 1 week apart. Cream was applied for approximately 3 hours under occlusion followed immediately by illumination using the Aktilite CL128 lamp, delivering red light at a dose of 37 J/cm^2.

Table 1-1 shows the incidence and severity of adverse drug reactions in these two trials.

Table 1-1: Incidence of Adverse Drug Reactions in ≥1% of Subjects with Actinic Keratoses in Studies PC T404/05 and PC T405/05 (Safety Population)

	METVIX & Aktilite PDT n = 126		Vehicle & Aktilite PDT n = 105	
	All Events*	**Severe**	**All Events***	**Severe**
Any Treatment Site Adverse Drug Reaction	113 (90%)	28 (22%)	48 (46%)	0 (0%)
Skin burning/pain/discomfort	109 (86%)	25 (20%)	38 (36%)	0 (0%)
Erythema	80 (63%)	7 (6%)	11 (10%)	0 (0%)
Scabbing/crusting/blister/erosions	36 (29%)	2 (2%)	1 (1%)	0 (0%)
Pruritus	28 (22%)	0 (0%)	8 (8%)	0 (0%)
Skin or eyelid edema	23 (18%)	2 (2%)	1 (1%)	0 (0%)
Skin exfoliation	17 (14%)	4 (3%)	3 (3%)	0 (0%)
Skin warm	5 (4%)	0 (0%)	2 (2%)	0 (0%)
Application site discharge	3 (2%)	0 (0%)	0 (0%)	0 (0%)
Skin hemorrhage	2 (2%)	0 (0%)	0 (0%)	0 (0%)
Skin tightness	2 (2%)	0 (0%)	0 (0%)	0 (0%)
Skin hyperpigmentation	2 (2%)	0 (0%)	0 (0%)	0 (0%)
Non Treatment Site Adverse Drug Reaction	13 (10%)	2 (2%)	0 (0%)	0 (0%)
Headache	3 (2%)	1 (1%)	0 (0%)	0 (0%)

*Mild, Moderate, or Severe

Less Common Clinical Trial Adverse Drug Reactions in Actinic Keratosis Studies Using METVIX c-PDT (<1%):

Eye disorders: eye pain, lacrimation increased
Gastrointestinal disorders: nausea
General disorders and administration site conditions: chills
Injury, poisoning and procedural complications: contusion
Nervous system disorders: dizziness
Skin and subcutaneous tissue disorders: hyperhidrosis

Another prospective, randomized, comparative, multicentre study (Study PC T311/01) included a total of 211 subjects, with 1 - 8 actinic keratosis lesions located on the face or scalp. Subjects were randomized to receive METVIX cream either once (Regimen I), or twice at one week apart (Regimen II). The cream was applied for approximately 3 hours under occlusion followed immediately by photodynamic therapy (PDT) using a light dose of 37 J/cm^2.

Table 1-2 shows the incidence and severity of adverse drug reactions in this trial.

Table 1-2: Incidence of Adverse Drug Reactions in ≥1% of Subjects with Actinic Keratosis in Study PC T311/01 (Safety Population)

	Treatment regimen			
	METVIX PDT Regimen I One Treatment (n=105)		METVIX PDT Regimen II Two Treatments One Week Apart (n=106)	
	All Events* n (%)	Severe n (%)	All Events* n (%)	Severe n (%)
Any Treatment Site Adverse Drug Reactions				
Burning sensation skin	16 (15%)	0 (0%)	20 (19%)	0 (0%)
Pain skin	9 (9%)	0 (0%)	19 (18%)	4 (3%)
Erythema	9 (9%)	1 (1%)	11 (10%)	0 (0%)
Edema skin	2 (2%)	0 (0%)	10 (9%)	1 (1%)
Stinging skin	6 (6%)	0 (0%)	3 (3%)	0 (0%)
Pricking skin sensation	1 (1%)	0 (0%)	7 (7%)	0 (0%)
Itching	2 (2%)	0 (0%)	4 (4%)	0 (0%)
Crusting	1 (1%)	0 (0%)	4 (4%)	0 (0%)
Photosensitivity toxic reaction	1 (1%)	0 (0%)	3 (3%)	2 (2%)
Skin ulceration	1 (1%)	0 (0%)	3 (3%)	0 (0%)
Erosion	2 (2%)	1 (1%)	0 (0%)	0 (0%)
Skin peeling	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	3 (3%)	0 (0%)
Eczema	0 (0%)	0 (0%)	2 (2%)	1 (1%)
Drug eruption	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Folliculitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Rash	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Eruption	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Non-treatment Site Adverse Drug Reactions				
Lip swelling	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Lip ulceration	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Allergic reaction	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Infection aggravated	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Inflammation localized	0 (0%)	0 (0%)	1 (1%)	0 (0%)

*Mild, moderate, severe

** Number (%) of subjects with at least one adverse drug reaction (i.e., if a patient reported the same reaction more than once, he/she was counted only once in the table)

Actinic Keratosis Studies Using METVIX DL-PDT:

In the two Phase III studies (Studies SPR.29102 and SPR.29112), a total of 231 patients with actinic keratosis were treated with METVIX DL-PDT on one side of the face and scalp. Of these 231 patients, 208 were treated with METVIX c-PDT and 23 with vehicle cream c-PDT on the contralateral side. Patients had 5-36 and 5-23 lesions per side in Studies SPR.29102 and SPR.29112, respectively. Local adverse drug reactions were reported less frequently on METVIX

DL-PDT than on c-PDT treated sides (45.0% and 60.1% of subjects, respectively) (see Table 1-3). No new local adverse drug reactions were reported. METVIX DL-PDT was associated with significantly less pain compared to METVIX c-PDT (see Clinical Trials).

Table 1-3 shows the incidence rates of adverse drug reactions in ≥1% of patients in the combined safety population of these two trials.

Table 1-3: Incidence of Adverse Drug Reactions in ≥1% of Subjects with Actinic Keratosis in European and Australian Studies (Safety Population)

	METVIX DL-PDT Treated Side (N=231)	METVIX c-PDT Treated Side (N=208)	Vehicle c-PDT Treated Side (N=23)	Unspecific Treated Side (N=231)
System Organ Class/Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All Adverse Drug Reactions	104 (45.0%)	125 (60.1%)	7 (30.4%)	6 (2.6%)
Infections and Infestations	1 (0.4%)	2 (1.0%)	-	-
Rash pustular	1 (0.4%)	2 (1.0%)	-	-
Skin and Subcutaneous Tissue Disorders	104 (45.0%)	124 (59.6%)	7 (30.4%)	-
Dermatitis	1 (0.4%)	1 (0.5%)	1 (4.3%)	-
Erythema	33 (14.3%)	44 (21.2%)	4 (17.4%)	-
Pain of skin	12 (5.2%)	17 (8.2%)	-	-
Photosensitivity reaction	15 (6.5%)	18 (8.7%)	1 (4.3%)	-
Pruritus	13 (5.6%)	17 (8.2%)	1 (4.3%)	-
Scab	21 (9.1%)	25 (12.0%)	-	-
Skin burning sensation	12 (5.2%)	18 (8.7%)	-	-
Skin erosion	-	5 (2.4%)	-	-
Skin exfoliation	2 (0.9%)	4 (1.9%)	1 (4.3%)	-
Skin hemorrhage*	7 (3.0%)	8 (3.8%)	1 (4.3%)	-
Skin irritation	1 (0.4%)	2 (1.0%)	-	-
Skin edema	2 (0.9%)	2 (1.0%)	-	-
Skin reaction	24 (10.4%)	30 (14.4%)	-	-

* this term includes post-procedural hemorrhage, hemorrhage and skin hemorrhage

Less Common (<1%) Clinical Trial Adverse Drug Reactions in Actinic Keratosis Studies Using METVIX DL-PDT:

Eye disorders: eye irritation, eye pain, eye swelling, eyelid edema, lacrimation increased
General disorders and administration site conditions: fatigue
Injury, poisoning and procedural complications: procedural dizziness
Nervous system disorders: headache
Skin and subcutaneous tissue disorders: blister, purpura, skin discomfort, skin swelling, skin tightness, swelling face

Superficial Basal Cell Carcinoma Study:

A total of 234 subjects were screened and 196 subjects enrolled in the pivotal superficial basal cell carcinoma study. Regarding drug adverse events, there were more events and more subjects in METVIX c-PDT group than in surgery group (37% subjects with 65 related adverse events versus 14.6% subjects with 21 related adverse events). Most related adverse events were dermatologic and more frequent in METVIX c-PDT group (34% subjects with 61 related dermatologic adverse events versus 7.3% subjects with 8 adverse events). These adverse events are summarised in Table 1-4.

Table 1-4: Incidence of Adverse Drug Reactions in ≥1% of Subjects in Superficial Basal Cell Carcinoma Study (Safety Population)

		METVIX (N=100)		Surgery (N=96)		
		Mild	Moderate	Mild	Moderate	Severe
Any Adverse Event		***26 (26.0%)***	***11 (11%)***	***10 (10.4%)***	***3 (3.1%)***	***1 (1.0%)***
General Disorders and Administration Site Conditions	Pain	1 (1%)	1 (1%)	-	-	1 (1.0%)
Infections and Infestations	**All**	**1 (1%)**	**-**	**3 (3.1%)**	**1 (1.0%)**	**1 (1.0%)**
	Application site infection	1 (1%)	-	-	-	-
	Wound infection	-	-	3 (3.1%)	1 (1.0%)	1 (1.0%)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	Basal cell carcinoma	-	1 (1%)	-	-	-
Nervous System Disorders	Headache	1 (1%)	-	-	-	-
Skin And Subcutaneous Tissue Disorders	**All**	**24 (24%)**	**9 (9%)**	**5 (5.2%)**	**1 (1.0%)**	**-**
	Milia	2 (2%)	-	-	-	-
	Photosensitivity reaction	22 (22%)	9 (9%)	-	-	-
	Skin hyperpigmentation	-	1 (1%)	-	-	-
	Erythema	-	-	3 (3.1%)	-	-
	Keloid scar	-	-	1 (1.0%)	-	-
	Pain of skin	-	-	-	1 (1.0%)	-
	Pruritus	-	-	1 (1.0%)	-	-
	Scar	-	-	1 (1.0%)	-	-
Injury, Poisoning and Procedural Complications	**All**	**-**	**-**	**4 (4.2%)**	**1 (1.0%)**	**-**
	Post procedural pain	-	-	2 (2.1%)	1 (1.0%)	-
	Wound dehiscence	-	-	2 (2.1%)	-	-
Musculoskeletal and Connective Tissue Disorders	Shoulder pain	-	-	1 (1.0%)	-	-
Surgical and Medical Procedures	**All**	**-**	**-**	**2 (2.1%)**	**-**	**-**
	Skin lesion excision	-	-	1 (1.0%)	-	-
	Suture insertion	-	-	1 (1.0%)	-	-

Related = possibly, probably or definitely related

The most commonly reported related adverse events were expected: photosensitivity reaction for METVIX c-PDT (31% subjects with 57 adverse events), and wound infection for surgery procedure (5.2% subjects with 5 adverse events). Among these subjects, there was 1 subject (1.7%) in surgery group who reported related adverse events of severe intensity. In the METVIX c- PDT group, the majority of related adverse events were of mild severity.

Abnormal Hematologic and Clinical Chemistry Findings

No abnormalities attributable to treatment with METVIX PDT have been observed. The results of repeated-dose toxicity studies indicated that the liver was the target organ for high intravenous doses of methyl aminolevulinate in rats, but examination of liver function tests from phase I trials in humans did not reveal any changes that were inconsistent with random variation.

Adverse Drug Reactions from Other Clinical Trials

In addition, there were reports of paresthesia, and, urticaria, rash, skin hypopigmentation, heat rash, and fatigue in Phase III studies in which METVIX c-PDT was performed with a different lamp (CureLight 01). There were also isolated reports of scar in a dose ranging study performed with CureLight where a relationship to treatment was uncertain.

Post-Market Adverse Drug Reactions

Application site eczema, allergic contact dermatitis, angioedema, eyelid edema, face edema (swelling face), hypertension, rash pustular (application site pustule) and urticaria have been described in post-marketing reports. Most skin reactions were localized to the treatment area and were not severe; some cases of erythema and swelling have been more extensive or serious.

DRUG INTERACTIONS

Overview

There have been no studies of the interaction of METVIX with other drugs, including local anesthetics. It is possible that concomitant use of other known photosensitizing agents might increase photosensitivity reactions when treated with METVIX cream.

The demographic of the treated population is largely elderly patients receiving a variety of concomitant systemic medications, and there is no suggestion of any interaction between METVIX PDT and these medications.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

This product is not intended for application by patients or unqualified medical personnel; therefore, this product is only dispensed to physicians. Use of METVIX cream without subsequent photodynamic therapy (c-PDT or DL-PDT) is not recommended.

Recommended Dose and Dosage Adjustment

METVIX c-PDT for Actinic Keratosis and Superficial Basal Cell Carcinoma

Actinic Keratosis: For treatment of thin or non-hyperkeratotic and non-pigmented actinic keratosis lesions on the face and scalp, one treatment session with METVIX c-PDT using red LED light should be performed. The treated lesions should be evaluated after 3 months and if needed, one additional treatment session can be performed. Multiple lesions can be treated in one session. METVIX c-PDT is not recommended for treatment of Grade III hyperkeratotic lesions. A maximum of 2 g of METVIX cream per treatment session should be applied.

Superficial Basal Cell Carcinoma (outside the H-zone of the face): One treatment session with METVIX c-PDT using red LED light should be performed with a second treatment session 7 days later. The treated lesions should be evaluated after 3 months, and if needed, two additional treatment sessions 7 days apart should be performed. A maximum of 2 g of METVIX cream per treatment session should be applied.

METVIX DL-PDT for Actinic Keratosis

For treatment of thin or non-hyperkeratotic and non-pigmented actinic keratosis lesions on the face and scalp, one treatment session with METVIX-PDT using daylight should be performed. The treated lesions should be evaluated after 3 months and if needed, one additional treatment session can be performed. METVIX DL-PDT is not recommended for treatment of Grade III (severe) hyperkeratotic lesions. A maximum of 2 g of METVIX cream per treatment session should be applied.

Missed Dose

If the patient for any reason cannot have the red light treatment 3 hours after METVIX application, the cream should be rinsed off. The patient should be instructed to protect the exposed area from sunlight, and prolonged or intense light for two days.

Administration

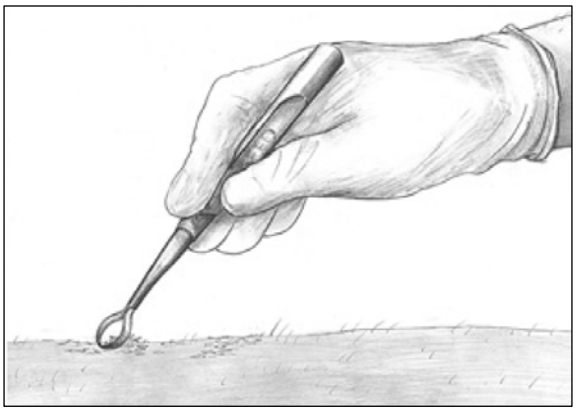
METVIX c-PDT for Actinic Keratosis and Superficial Basal Cell Carcinoma

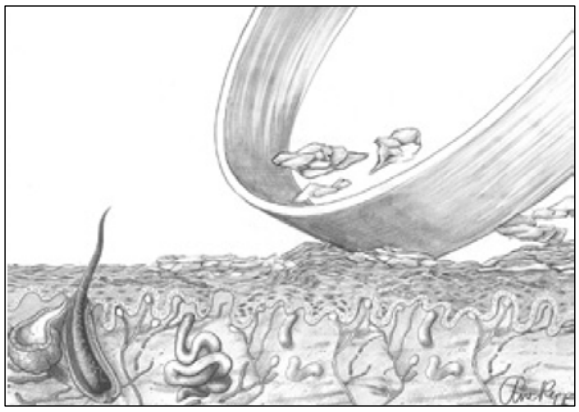
All steps below are to be performed by a healthcare professional wearing nitrile gloves and universal precautions should be taken. Vinyl and latex gloves do not provide adequate protection when using this product. One METVIX c-PDT session consists of:

1) Lesion debriding

Before applying METVIX cream, the surface of the lesions should be prepared with a small dermal curette to remove scales and crusts and to roughen the surface of the lesion (Fig. 1 and Fig. 2). This is to facilitate access of the cream and light to all parts of the lesion.

Figure 1 Figure 2





2) Application of METVIX cream

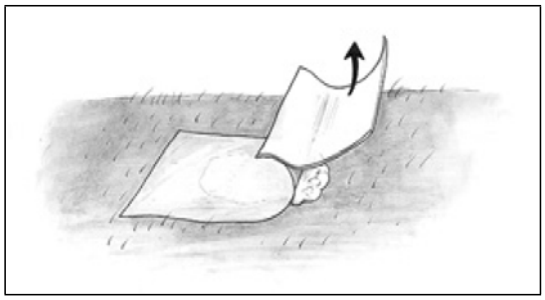
Using a spatula, apply a layer of METVIX cream about 1 mm thick to the lesion and the surrounding 5 mm of normal skin. Multiple lesions may be treated during the same treatment session. Each treatment field should be limited to the size of the light field of the lamp.

3) Cover the lesion(s)

The area to which the cream has been applied should then be covered with an occlusive, non-absorbent dressing (Fig. 3). After cream application, patients should avoid exposure of the treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) prior to red light treatment. Exposure to other light sources may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Patients should protect treated areas from the sun by wearing a wide-brimmed hat, protective clothing or similar covering of light-opaque material.

Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the METVIX cream outside the treatment site to the eyes or surrounding skin. The treated site should be protected from extreme cold with adequate clothing or by remaining indoors between the application of METVIX cream and the PDT light treatment.

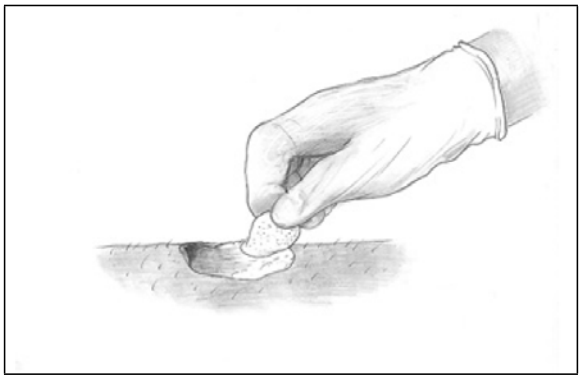
Figure 3



4) Wait for 3 hours (at least 2.5 hours, but no more than 4 hours) (see Warnings and Precautions)
METVIX cream should not be applied for longer than the recommended time. If PDT cannot be performed on the patient after the application of METVIX cream, the cream should be rinsed off with saline and gauze and treated areas should be protected from sunlight and prolonged and intense light for 2 days.

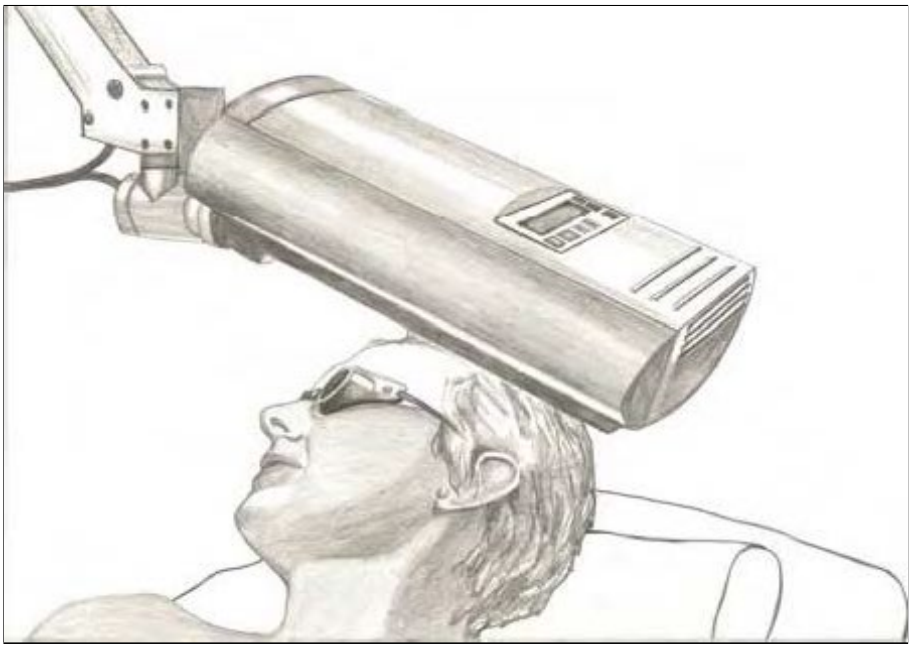
5) Removal of Dressing and Rinse Off Excess Cream
Following removal of the occlusive dressing, clean the area with saline and gauze (Fig. 4).

Figure 4



6) Illumination of METVIX Treated Lesion (see Warnings and Precautions)
It is important to ensure that the correct light dose is administered. The light intensity at the lesion surface should not be higher than 200 mW/cm^2. Patient and operator should adhere to safety instructions and precautions provided with the lamp. The patient and operator should wear protective goggles during illumination. The lamp should be carefully positioned so that dosing is accurate and immediately thereafter the lesion should be exposed to red light at 630 nm and a total light dose of 37 J/cm^2 (Fig. 5).

Figure 5



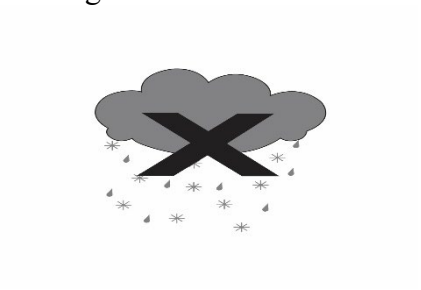
Patients should be advised that transient stinging and/or burning at the target lesion sites may occur during the period of light exposure. It is not necessary to protect healthy skin surrounding the lesions during exposure.

If red light treatment is interrupted or stopped for any reason, it may be restarted. METVIX cream is not intended for use with any device other than the approved lamp: Aktilite CL 128.

METVIX DL-PDT for Actinic Keratosis

METVIX DL-PDT can be used if the temperature conditions (ideally >10°C and <35°C) are suitable to stay comfortably outdoors for 2 hours. Daylight conditions may not be sufficient for METVIX DL-PDT from November to March. If the weather is rainy, snowy or is likely to become so, METVIX DL-PDT should not be used.

Figure 6



One treatment session using daylight consists of:

1) Sunscreen Application: Sunscreen should be applied to all sun exposed areas, including the treatment areas, prior to lesion preparation. Sunscreen used should offer adequate protection (SPF30 or higher) and must 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.

2) Lesion debriding: Once sunscreen has dried and before applying METVIX cream, the surface of the lesions should be prepared with a small dermal curette to remove scales and crusts and to roughen the surface of the lesion (Fig.1 and Fig.2). This is to facilitate access of the cream and light to all parts of the lesion.

3) Application of METVIX cream: Healthcare professionals should wear nitrile gloves during this step and universal precautions should be taken. Vinyl and latex gloves do not provide adequate protection when using this product. Using a spatula, apply a thin layer (about 1 mm) of METVIX to the treatment areas. Multiple lesions may be treated during the same treatment session.

4) No occlusion is necessary.

5) Daylight therapy: Patients should go outside after METVIX application or, at the latest, 30 minutes later in order to avoid excessive protoporphyrin IX accumulation which would lead to greater pain on light exposure.

6) In order to minimize pain and ensure maximum efficacy the patient should then stay outdoors for 2 continuous hours in full daylight and avoid going indoors. On sunny days, should the patient feel uncomfortable in direct sunlight, shelter in the shade may be taken. Patients should make sure the treated area is continuously exposed to daylight and not covered.

7) Rinse Off Excess Cream: Following the 2-hour exposure period, patients should be instructed to wash the METVIX off with soap and water.

OVERDOSAGE

METVIX cream: METVIX cream overdose has not been reported in clinical trials or in post-marketing experience and is not likely to occur in clinical practice due to the nature of the treatment being administered directly by a physician.

No incidences of oral ingestion of METVIX cream have been reported. In the unlikely event that the drug is ingested, monitoring and supportive care is recommended. Methyl aminolevulinate has a low order of single-dose oral and intravenous toxicity in mice and rats; the minimally lethal oral acute dose was more than 2000 mg/kg.

Red Light: There is no information on overdose of red light following METVIX cream application. If red light overexposure and a skin burn occurs, the patient should be treated according to standard practice for the treatment of cutaneous burns.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Photosensitization occurs through the metabolic conversion of methyl aminolevulinate (prodrug) to photoactive porphyrins (PAP), which accumulates in the skin lesions where METVIX cream has been applied. When exposed to light of appropriate wavelength and energy, the accumulated photoactive porphyrins produce a photodynamic reaction, resulting in an oxygen dependent cytotoxic process. The absorption of light causes an excited state of the porphyrin molecules, and subsequent spin transfer from photoactive porphyrins to molecular oxygen generates singlet oxygen, which can further react to form superoxide and hydroxyl radicals. Photosensitization of lesions using METVIX cream, plus illumination with Aktilite CL 128 (630 nm wavelength red light) at 37 J/cm^2, is the basis for METVIX photodynamic therapy.

When METVIX is used with daylight, protoporphyrin IX is continuously being produced and activated within the target cells during the 2 hours of daylight exposure creating a constant micro-phototoxic effect.

Pharmacodynamics

See Mechanism of Action above.

Pharmacokinetics

Absorption: *In vitro* dermal absorption of radiolabelled methyl aminolevulinate applied to human cadaver 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 compromised human skin (damage similar to actinic keratosis, BCC, roughened surfaces or without stratum corneum) were performed.

There is no information on the pharmacokinetics of methyl aminolevulinate in human serum due to the instability of the drug in serum.

Metabolism, distribution and elimination: The metabolic pathway in humans by which photoactive porphyrins are produced from methyl aminolevulinate is not fully elucidated.

In humans, the levels of photoactive porphyrins in the skin were indirectly determined through a semi-quantitative method measuring the skin fluorescence following methyl aminolevulinate application. A higher degree of accumulation of photoactive porphyrins in lesions compared to normal skin has been demonstrated after topical application of methyl aminolevulinate.

After application of methyl aminolevulinate to the skin of human subjects for 3 hours, a subsequent illumination with a narrow red light spectrum at 630 nm wavelength and a total light dose of 37 J/cm^2 reduced the fluorescence of skin lesions near pre-treatment levels immediately after illumination, but it did not result in complete photobleaching. Thereafter, an increase in fluorescence 2 hours following the illumination was observed. Complete photobleaching was observed 24 hours following the illumination.

Special Populations and Conditions

The pharmacokinetics of methyl aminolevulinate has not been investigated in conditions such as hepatic insufficiency, or renal insufficiency. Any systemic effects are considered to be negligible due to selective accumulation of the compound in lesions compared to normal skin and since systemic absorption is usually minimal after topical administration (see Adverse Reactions).

STORAGE AND STABILITY

Store refrigerated 2-8 ^oC.

Use contents within 3 months after opening. The product should not be used after 24 hours without refrigeration.

SPECIAL HANDLING INSTRUCTIONS

Contact sensitization (allergenicity) has been observed with the use of METVIX cream (see Adverse Reactions and Clinical Trials). Care should be taken by individuals handling METVIX cream to avoid inadvertent skin contact. Nitrile gloves should be worn when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection from this product.

DOSAGE FORMS, COMPOSITION AND PACKAGING

METVIX cream is an oil-in-water emulsion. METVIX cream contains methyl aminolevulinate hydrochloride equivalent to 168 mg/g of methyl aminolevulinate.

It also contains glyceryl monostearate, cetostearyl alcohol, polyoxyl stearate, cholesterol, and oleyl alcohol as emulsifying agents. It also contains glycerol, white soft paraffin, isopropyl myristate, arachis (peanut) oil, refined almond oil as emollients, edetate disodium as a chelating agent, methylparaben and propylparaben as preservatives, and purified water.

METVIX cream is packaged in a 2 gram aluminum tube sealed with an aluminum membrane and a screw cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

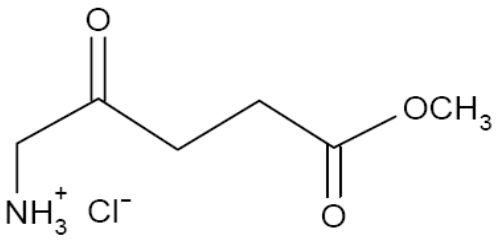
Proper name: methyl aminolevulinate hydrochloride

Chemical names: methyl 5-aminolevulinate hydrochloride,
5-aminolevulinic acid methyl ester hydrochloride,
5-amino-4-oxopentanoic acid methyl ester hydrochloride,
methyl 5-amino -4-oxopentanoate hydrochloride,
methyl 5-amino -4-oxovaleroate hydrochloride,
5-amino-4-oxovaleric acid methyl ester hydrochloride

Molecular formula: $C_6H_{11}NO_3 \bullet HCl$

Molecular mass: 181.62

Structural formula:



Physicochemical properties: Methyl aminolevulinate hydrochloride is a white to slightlyyellow powder that is freely soluble in water and methanol, soluble in ethanol, and practically insoluble in most organic solvents. Methyl aminolevulinate hydrochloride a weak acid; pKa = 8.1.

CLINICAL TRIALS

ACTINIC KERATOSIS USING METVIX c-PDT

Placebo-Controlled Studies

Study demographics and trial design

Studies PC T404/05 and PC T405/05 were placebo-controlled, double-blind, randomized, parallel-group Phase III studies designed to assess the safety and effectiveness of METVIX c-PDT for the treatment of actinic keratosis. A total of 211 randomized subjects with a total of 1555 non-hyperkeratotic actinic keratoses were studied. Patients were treated with METVIX c-PDT using the Aktilite CL128 lamp at the recommended dose of 37 J/cm^2. A second treatment session was

performed 7 days later. All patients in both studies were Caucasians. Gender, age, and skin type were similar in the two studies and were well balanced in the treatment groups within each study. Their other demographic characteristics are found in Table 2-1.

The subject complete response rate was assessed 3 months after the last treatment. Lesion clinical complete response was defined as complete disappearance of a lesion upon visual inspection and palpation. If all treated lesions within a subject were in clinical complete response 3 months after treatment, the subject was assessed as a complete responder.

Table 2-1: Patient Demographics in Placebo-Controlled Studies in Actinic Keratosis

	Study PC T404/05 (Study 1)			Study PC T405/05 (Study 2)			Overall		
	METVIX c-PDT n = 49	Vehicle c-PDT n = 47	Total n = 96	METVIX c-PDT n = 57	Vehicle c-PDT n = 58	Total n = 115	METVIX c-PDT n = 106	Vehicle c-PDT n = 105	Total n = 211
Gender n (%)									
Male	42 (86)	37 (79)	79 (82)	46 (81)	45 (78)	91 (79)	88 (83)	82 (78)	170 (81)
Female	7 (14)	10 (21)	17 (18)	11 (19)	13 (22)	24 (21)	18 (17)	23 (22)	41 (19)
Age (y)									
Mean	66.1	66.7	66.4	69.5	67.0	68.2	67.9	66.8	67.4
(SD)	(10.2)	(9.2)	(9.7)	(9.0)	(10.4)	(9.8)	(9.7)	(9.8)	(9.7)
Range	43 – 86	48 – 89	43 – 89	47 – 88	41 – 90	41 – 90	43 – 88	41 – 90	41 – 90
Number (%) of patients aged ≤65 and >65 years									
≤65 y	21 (43)	22 (47)	43 (45)	13 (23)	28 (48)	41 (36)	34 (32)	50 (48)	84 (40)
>65 y	28 (57)	25 (53)	53 (55)	44 (77)	30 (52)	74 (64)	72 (68)	55 (52)	127 (60)
Number (%) of patients with each skin type									
I	12 (24)	10 (21)	22 (23)	10 (18)	12 (21)	22 (19)	22 (21)	22 (21)	44 (21)
II	22 (45)	26 (55)	48 (50)	28 (49)	23 (40)	51 (44)	50 (47)	49 (47)	99 (47)
III	12 (24)	10 (21)	22 (23)	13 (23)	18 (31)	31 (27)	25 (24)	28 (27)	53 (25)
IV	3 (6)	1 (2)	4 (4)	6 (11)	5 (9)	11 (10)	9 (8)	6 (6)	15 (7)

Study results

Table 2-2 shows patient complete response data. In all studies, METVIX-PDT was clearly superior to Vehicle-PDT in regards to patient complete response ($p<0.0001$).

Table 2-2: Patients with Complete Response - Placebo-Controlled Studies

	Study 1		Study 2	
	METVIX c-PDT n = 49	**Vehicle c-PDT n = 47**	**METVIX c-PDT n = 57**	**Vehicle c-PDT n = 58**
Subjects with Complete Response	29 59.2%	7 14.9%	39 68.4%	4 6.9%

Table 2-3 shows the lesion complete response rates. In all studies, the lesion response rates were higher for METVIX-PDT than for Vehicle-PDT.

Table 2-3: Lesion Complete Response in Placebo-Controlled Studies

		Study 1		Study 2	
		METVIX c-PDT n=363	**Vehicle c-PDT n=360**	**METVIX c-PDT n=418**	**Vehicle c-PDT n=414**
Lesions with Complete Response		313 (86%)†	188 (52%)	348 (83%)†	119 (29%)
Grade 1		**259**	**267**	**182***	**161**
Face	Total	191	201	99	88
	CR	167 (87%)	121 (60%)	90 (91%)	33 (38%)
Scalp	Total	68	66	76	73
	CR	63 (93%)	29 (44%)	66 (87%)	31 (42%)
Grade 2		**104**	**93**	**236***	**253**
Face	Total	76	68	119	157
	CR	65 (86%)	29 (43%)	103 (87%)	35 (22%)
Scalp	Total	28	25	115	96
	CR	18 (64%)	9 (36%)	89 (77%)	20 (21%)

† $p<0.0001$

* The ITT population of Study 2 included 1 patient in the METVIX-PDT group with 9 lesions on the hands; seven grade 1 lesions (4% of all grade 1 lesions in this group) and two grade 2 lesions (1% of all grade 2 lesions). These lesions are included in the overall number of grade 1 and 2 lesions.

CR = complete response

There was no difference between response rates to METVIX c-PDT for Grade 1 lesions on the face and scalp (CR rates of 89 % and 90 % respectively). For Grade 2 lesions, the corresponding CR rates to METVIX c-PDT were 86 % and 75 % respectively.

Active-Controlled Studies

Study demographics and trial design

An open, non-inferiority, randomized study (Study PC T311/01) was conducted to compare two treatment regimens of METVIX c-PDT in patients with clinically confirmed AK lesions (average of 2 lesions/patient, range: 1-8) on the face or scalp. A total of 211 patients with 413 lesions were included in the study. METVIX cream was applied for 3 hours before illumination with a LED light source with an average wavelength of 630 nm and a light dosage of 37 J/cm^2.

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

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

All patients were clinically assessed three months after their final METVIX treatment.

All patients in this study were Caucasians. Gender, age, and skin type were similar in the two treatment groups.

Table 2-4: Patient Demographics - Study PC T311/01

	Regimen I n=105	Regimen II n=106
Gender n (%)		
Male	41 (39)	41 (39)
Female	64 (61)	65 (61)
Age (years)		
Mean (SD)	69 (10)	68 (11)
Range	44-91	44-96
Skin Type n (%)		
I	7 (7)	8 (8)
II	59 (56)	58 (55)
III	27 (26)	31 (29)
IV	9 (9)	7 (7)
V	3 (3)	2 (2)

Study results

Patient complete response rates (i.e., the proportion of patients where all lesions had shown complete clinical response) and lesion complete response rates for each treatment group are presented in Tables 2-5 and 2-6, respectively.

Table 2-5: Patients with Complete Response – Study PC T311/01

Regimen I		Regimen II	
At study end PP and ITT* N=105	After one session only PP and ITT* N=105	At study end PP* N=100	At study end ITT* N=106
93 (89%)[1]	77 (73%)	80 (80%)	83 (78%)

*PP = Per protocol analysis; ITT = Intent-to-Treat Analysis. ITT and PP were the same for Regimen I.
[1]Includes 27% of patients with re-treatment at 3 months

At study end, Regimen I was found to be non-inferior to Regimen II on the primary endpoint of patient complete response rate, within less than 1%, much below the pre-defined non-inferiority margin of 15%.

Table 2-6: Lesion Complete Response– Study PC T311/01

	Regimen I		Regimen II	
	At Study end PP and ITT*	**After one session only PP and ITT***	**At Study end PP***	**At study end ITT***
Overall (face & scalp, Grade 1 & Grade 2)	183/198 (92%)	161/198 (81%)	175/202 (87%)	185/215 (86%)
Grade I	96/99 (97%)	92/99 (93%)	76/85 (89%)	85/95 (89%)
Face	90/93 (97%)	86/93 (92%)	71/79 (90%)	80/89 (90%)
Scalp	6/6 (100%)	6/6 (100%)	5/6 (83%)	5/6 (83%)
Grade 2	87/99 (88%)	69/99 (70%)	95/113 (84%)	95/115 (83%)
Face	81/91 (89%)	65/91 (71%)	79/93 (85%)	79/95 (83%)
Scalp	6/8 (75%)	4/8 (50%)	16/20 (80%)	16/20 (80%)

*PP = Per protocol population; ITT = Intent-to-treat population. ITT and PP were the same for Regimen I.

ACTINIC KERATOSIS USING METVIX DL-PDT

Study demographics and trial design

The efficacy and safety of METVIX daylight photodynamic therapy (DL-PDT) was compared to METVIX conventional photodynamic therapy (c-PDT) in two randomized, investigator-blinded, comparative, intra-individual clinical studies conducted in Europe (Study SPR.29112) and Australia (Study SPR.29102), including a total of 231 patients with actinic keratosis. Of these patients, a small group of 23 patients with actinic keratosis was included in the European study to compare METVIX DL-PDT with vehicle c-PDT.

Subjects in the European study (n=131) were predominantly male (92%), with a mean age of 73.0 years (range: 47 to 91 years) and all but 1 were Caucasian. Subjects in the Australian study (n=100) were also predominantly male (75%), with a mean age of 66.9 years (range 42 to 90 years); all subjects were Caucasian. Subjects in the European study tended to be slightly darker-skinned (predominantly skin phototype II) compared to subjects in the Australian study (predominantly skin phototype I, see Table 2-7).

Table 2-7: Patient Demographics and Disease Characteristics – Studies SPR.29102 and SPR.29112 (ITT Population)

	European study SPR.29112 (N=131)*		Australian study SPR.29102 (N=100)	
Gender				
Male	121 (92.4%)		75 (75.0%)	
Female	10 (7.6%)		25 (25.0%)	
Age (years)				
Mean (SD)	73.0 (9.5)		66.9 (10.5)	
Range	(47, 91)		(42, 90)	
Number (%) of patients aged <65 and ≥65 years				
<65 y	21 (16.0%)		41 (41.0%)	
≥65 y	110 (84.0%)		59 (59.0%)	
Number (%) of patients with each skin type				
I	11 (8.4%)		56 (56.0%)	
II	86 (65.6%)		33 (33.0%)	
III	27 (20.6%)		11 (11.0%)	
IV	7 (5.3%)		0 (0%)	
	METVIX DL-PDT treated side**	**METVIX c-PDT treated side****	**METVIX DL-PDT treated side**	**METVIX c-PDT treated side**
Number of lesions treated	957	960	1379	1372
Face	483 (50.5%)	500 (52.1%)	1038 (75.3%)	1011 (73.7%)
Scalp	474 (49.5%)	460 (47.9%)	341 (24.7%)	361 (26.3%)
Severity of lesions treated				
Mild	554 (57.9%)	555 (57.8%)	1335 (96.8%)	1322 (96.4%)
Moderate	403 (42.1%)	405 (42.2%)	44 (3.2%)	50 (3.6%)

* Includes Group 1 (n=108): METVIX DL-PDT vs METVIX c-PDT and Group 2 (n=23): METVIX DL-PDT vs Vehicle c-PDT
** Group 1 (n=108): METVIX DL-PDT vs METVIX c-PDT patients

The actinic keratosis lesions in the European study were defined as "mild" (slightly palpable, better felt than seen) or "moderate" (moderately thick, easily felt and seen), while those in the Australian study were confined to "mild". In the European study, there was a slightly higher percentage of total mild lesions treated overall (58% mild on both sides, compared to 42% moderate on both sides) and patients had on average 9 lesions/side (range: 5-23). In the Australian study, most lesions were mild on both sides (approximately 96%) and patients had on average 14 lesions/side (range 5-36). For both studies, the number, localization and severity of lesions were similar between treated sides (see Table 2-7).

The primary efficacy objective in the two studies was to show the non-inferiority of METVIX DL-PDT versus METVIX c-PDT in terms of subject-lesion complete response rate (defined as the percentage change from baseline in the total number of treated lesions per side) at Week 12 after a single treatment, in patients with mild and/or moderate actinic keratosis for the European study and mild actinic keratosis for the Australian study. A co-primary safety objective of subject assessment

of maximal pain during the first treatment session was also included in both studies. Subject-side complete response (defined as the complete clearance of all lesions on one treatment side) was a key secondary endpoint in both studies. Patients were treated on one side of the face or scalp with Metvix DL-PDT and on the contralateral side with Metvix c-PDT using the Aktilite CL128 lamp on Day 1. In the Australian study, a second treatment was allowed at Week 12 for lesions with no response or new lesions. In the European study, a comparison of METVIX DL-PDT to vehicle c-PDT was made using subject-lesion response in order to assess the sensitivity of the study to detect differences.

Study results

The results of both studies demonstrated that METVIX DL-PDT is non-inferior to METVIX c-PDT for treating actinic keratosis lesions based on the percentage change from baseline in complete response by subject-lesions at 12 weeks after one treatment (see Table 2-8).

In the European study, the mean percentage change of complete response by subject-lesion (mild and moderate) from baseline was 70.1% versus 73.6% for DL-PDT sides versus c-PDT sides respectively (95% CI of the mean treatment difference: [-9.5; 2.4], per protocol population: n=96). In the Australian study, the mean percentage change of complete response by subject-lesion (mild lesions only) from baseline was 89.2% versus 92.8% for DL-PDT sides versus c-PDT sides respectively (95% CI of the mean treatment difference: [-6.8; -0.3], per protocol population: n=90).

In both studies, complete response rates by subject-side (100% lesion clearance on one treatment side) were lower than lesion response rates due to the high number of lesions per side. In the European study, which included a higher proportion of moderate lesions compared to the Australian study, the complete response rate by subject-side was 15.7% versus 24.1% for DL-PDT sides versus c-PDT sides, respectively (ITT population: n=108). In the Australian study, the complete response rate by subject-side was 49.5% versus 62.6% for the DL-PDT sides versus c-PDT sides, respectively.

Table 2-8: Mean Percentage Change of Complete Response by Subject-Lesion and Complete Response Rate by Subject-Side at Week 12

		European study SPR.29112 [(1)]		Australian study SPR.29102[(1)]	
		METVIX DL-PDT treated side	**METVIX c-PDT treated side**	**METVIX DL-PDT treated side**	**METVIX c-PDT treated side**
Primary endpoint: complete response by subject-lesion [(1)]					
PP*	N	96	96	90	90
	Mean (SD)	70.1 (27.4)	73.6 (25.5)	89.2 (15.0)	92.8 (14.1)
	Treatment difference (SD): (METVIX DL-PDT) – (METVIX c-PDT), [95% CI]	-3.5 (29.3) [-9.5; 2.4]		-3.5 (15.6) [-6.8 ; -0.3]	
ITT/ Worst-case*	N	108	108	98	98
	Mean (SD)	68.4 (27.7)	71.5 (27.6)	86.5 (21.3)	89.9 (21.0)
Secondary endpoint: complete response rate by subject-side					
ITT/ Worst-case*	N	108	108	99	99
	Complete response (rate)	17 (15.7%)	26 (24.1%)	49 (49.5%)	62 (62.6%)

*PP=Per protocol analysis; ITT/Worst-case=Intent to Treat analysis, with missing values considered as 'Non Complete Response'
[(1)] Mild and moderate lesions for Study SPR.29112 and mild lesions for Study SPR.29102

Based on patient assessment of maximal treatment-related pain (on an 11-point scale ranging from 0 to 10) during the first treatment session, METVIX DL-PDT was significantly less painful compared to METVIX c-PDT, with a pain score of 0.8 (SD: 1.2) versus 5.7 (SD: 2.3) ($p<0.001$) in the Australian study and 0.7 (SD: 1.3) versus 4.4 (SD: 2.8) ($p<0.001$) in the European study.

In the European study in the small group of 23 patients included to compare METVIX DL-PDT to vehicle c-PDT , the mean percentage change of complete response by subject-lesion from baseline was 78.3% with METVIX DL-PDT and 61.2% with vehicle c-PDT ($p=0.005$), confirming the sensitivity of the study to detect differences. The complete response rate by subject-side was 21.7% with METVIX DL-PDT and 13.0% with Vehicle c-PDT ($p=0.32$).

In both studies, regardless of whether the weather was sunny or cloudy, efficacy was demonstrated.

SUPERFICIAL BASAL CELL CARCINOMA USING METVIX c-PDT

Study demographics and trial design

One pivotal Phase III study involving patients with primary superficial basal cell carcinoma (BCC) outside the facial H-zone was performed (Study 29040). In this study, response rates in 100 patients treated with METVIX c-PDT in combination with the Aktilite CL128 lamp were compared with those in 96 patients treated with excision surgery.

A total of 196 subjects were enrolled in the 27 sites of whom 66 (33.7%) were female and 130 (66.3%) were male. The mean age was 63.8 years (range 31 to 92 years). All subjects were Caucasian. Of the 196 subjects comprising the Intent to Treat (ITT) and safety populations, 100

were randomized to METVIX c-PDT and 96 to excision surgery. There were no notable differences between the treatment groups with respect to demographic characteristics (see Table 2-9). Twenty three (11.7%) subjects discontinued the study and a further 14 (7.1%) subjects were excluded from the Per Protocol (PP) analysis. The PP population comprised 96 subjects randomized to METVIX c-PDT and 86 subjects randomized to excision surgery.

Table 2-9 Patient Demographic Data for Superficial Basal Cell Carcinoma Study (ITT)

		METVIX c-PDT	Surgery	TOTAL
Gender	**N**	100 (100%)	96 (100%)	196 (100%)
	Male	64 (64.0%)	66 (68.8%)	130 (66.3%)
	Female	36 (36.0%)	30 (31.3%)	66 (33.7%)
Age (in Years)	**N**	100	96	196
	Mean (SD)	64.5 (12.7)	63.1 (13.9)	63.8 (13.3)
	Median	68.5	66.5	67
	(Min, Max)	(33,85)	(31,92)	(31,92)
Race	**N**	100 (100%)	96 (100%)	196 (100%)
	Caucasian	100 (100.0%)	96 (100.0%)	196 (100.0%)
Lesion Diameter (mm)	**N**	100	94	
	Mean (SD)	12.5 (3.7)	12.6 (3.7)	
Number of lesions per patient	**N**	100	96	
	Median	1.0	1.0	
Lesion Distribution	**01**	79 (79%)	77 (80.2%)	
	02	11 (11%)	8 (8.3%)	
	03	7 (7%)	7 (7.3%)	
	04	2 (2%)	2 (2.1%)	
	05	1 (1%)	2 (2.1%)	

N = Number of subjects evaluable
SD = standard deviation

The primary efficacy variable was the percentage reduction in lesion count per subject 3 months after last treatment. The lesion response was defined as Complete Response (CR; complete clearance of lesion) or Non Complete Response (Non CR; non complete clearance of lesion).

The secondary efficacy variables comprised:

- Cosmetic outcome assessed by the investigator 3, 6 and 12 months after last treatment.
- Percentage reduction in lesion count per subject 6 and 12 months after last treatment.

Lesion preparation, METVIX cream application, and illumination procedures were similar to those for the actinic keratosis trials described in the monograph and performed in a standardized manner in all three studies. Assessed efficacy parameters were also similar to those for the actinic keratosis trials.

Study results

Three months after treatment, the reduction in lesion count per subject was more than 90% in the PP population of the METVIX c-PDT and surgery treatment groups with rates of 92% and 99% respectively. The results for the ITT population with last observation carried forward are almost identical for the two treatment groups (87.4% and 89.4% respectively). The key results are shown in Table 2-10.

Table 2-10: Reduction in Lesion Count Per Subject of METVIX c-PDT Compared with Surgery 3 months after Last Treatment

Population	Percentage Reduction in Lesion Count			
		METVIX c-PDT	**Surgery**	**95% CIs**
PP	Ls mean ± Std err Mean ± sd	**n=96** 92.2 ± 1.8 94.5 ± 21.1	**n=86** 99.2 ± 1.9 99.4 ± 5.4	[-12.1;-1.9]
ITT-LOCF	Ls mean ± Std err Mean ± sd	**n=100** 87.4 ± 3.1 90.8 ± 27.8	**n=96** 89.4 ± 3.1 90.1 ± 29.6	[-10.6;6.6]

PP – per protocol ITT – intent to treat
LOCF – last observation carried forward CI – confidence intervals
LS – least square
Std err – standard error
sd – standard deviation

With regard to secondary outcomes, the efficacy of surgery was superior to that of METVIX c-PDT from Month 6 after the last treatment onwards. For the ITT-LOCF population, the average reduction in lesion count by subject was 84 % in the METVIX c-PDT versus 92 % in the surgery group, 6 months after the last treatment (p=0.043) and 79 % versus 92 %, 12 months after the last treatment (p=0.004). For lesions in CR at 3 months, 91 % remained in CR at 12 months versus 100 % after surgery.

Cosmetic outcome was assessed by the investigator for each lesion that had responded completely with regard to occurrence of the following signs or symptoms: scarring, atrophy, induration, redness or change in pigmentation. Three and 6 months after the last treatment, cosmetic outcome in METVIX c-PDT group was superior to that of the surgery group ($p<0.001$). Please see Table 2-11 for details. Twelve months after last treatment, the investigator assessed cosmetic outcome was superior for the METVIX c-PDT group compared to that of the surgery group ($p<0.001$), i.e., 92.8% of the subjects were considered success in METVIX c-PDT group compared with 51.2% of the subjects in surgery group. Twelve months after the last treatment, 64.7% of lesions had an excellent cosmetic outcome with METVIX c-PDT versus 18.8% with surgery. No poor cosmetic outcomes were observed in METVIX c- PDT group whereas 5 (4.8%) were rated as poor for the surgery group.

Table 2-11: Cosmetic outcome assessed by investigator 3, 6, and 12 months after the last treatment

		METVIX c-PDT	Surgery	p-value(1)
Month-3 After (observed cases)	N Success Failure	92 (100.0%) 78 (84.8%) 14 (15.2%)	87 (100.0%) 44 (50.6%) 43 (49.4%)	<0.001
Month-6 After (observed cases)	N Success Failure	88 (100.0%) 83 (94.3%) 5 (5.7%)	87 (100.0%) 45 (51.7%) 42 (48.3%)	<0.001
Month 12 After (observed cases)	N Success Failure	83 (100.0%) 77 (92.8%) 6 (7.2%)	86 (100.0%) 44 (51.2%) 42 (48.8%)	<0.001

(1) p-values were obtained from CMH test stratified by pseudo-centre using Ridit score
Success = excellent or good cosmetic outcome
Failure= fair or poor cosmetic outcome

DETAILED PHARMACOLOGY

Non Clinical Pharmacodynamics: The mode of action of methyl aminolevulinate has been shown in pharmacodynamic studies conducted in tumour cell lines *in vitro* and in the nude mouse normal skin model *in vivo* as well as in the scientific literature. After topical application of methyl aminolevulinate, porphyrins accumulate intracellularly in the treated skin lesions. The intracellular porphyrins (including protoporphyrin IX) are photoactive, fluorescing compounds and, upon light activation in the presence of oxygen, singlet oxygen is formed that causes damage to cellular compartments, in particular the mitochondria. This photochemical reaction results in phototoxicity in the light-exposed target cells.

Non Clinical Pharmacokinetics: The dermal penetration of methyl aminolevulinate through skin was investigated *in vitro* in skin excised from rats and humans. Use of radiolabelled methyl aminolevulinate in topical application in rats for 48 hours resulted in 13.1% and 6.4% systemic absorption through abraded and non-abraded skin respectively. The fraction remaining at the skin application site of rats was quantified to be 6.3% (abraded) and 8.4% (non-abraded) after 24 hours exposure. In contrast, *in vitro* dermal absorption of radiolabelled methyl aminolevulinate applied to human cadaver skin in a dermal penetration cell (Franz cell) showed that after 24 hours, the mean cumulative absorption through human skin was only 0.26% of the administered dosed. A skin depot containing 4.9% of the dose was formed. No corresponding studies in compromised human skin (damage similar to actinic keratosis, sBCC, roughened surfaces or without stratum corneum) were performed.

Clinical Pharmacology: The pharmacokinetics of methyl aminolevulinate cream after topical application in humans *in vivo* was investigated using the natural fluorescence of photoactive porphyrins (PAPs). The penetration and accumulation of methyl aminolevulinate and PAPs in lesions and normal skin of patients with actinic keratosis (AK) and basal cell carcinoma (BCC) were investigated in two clinical studies. In one study, fluorescence microscopy of lesion biopsies was performed and in the other study, surface fluorescence of lesions and treated normal skin was measured.

Absorption in most lesions achieved a plateau within a few hours. The depth and extent of accumulation of PAPs was greatest with the highest concentration tested (168 mg/g). Increasing the duration of application beyond 10 to 12 hours made little difference to the depth of penetration of fluorescence in the lesion, but increases fluorescence in adjacent normal skin.

There was clear evidence of selective localization in lesions relative to surrounding normal skin. Accumulated PAPs appear to be retained in the lesions for many hours after cream application, but subsequent illumination with non-coherent light of 570-670 nm wavelength and a total light dose of 75 J/cm^2 resulted in complete photobleaching with levels of porphyrins returning to pre- treatment levels. Illumination with red light with a narrow spectrum at 630 nm and a total light dose of 37 J/cm^2 reduced the fluorescence of skin lesions near pre-treatment levels immediately after illumination, but it did not result in complete photobleaching. Thereafter, an increase in fluorescence 2 hours following the illumination was observed. Complete photobleaching was observed 24 hours following the illumination.

The systemic absorption of methyl aminolevulinate in humans has not been properly assessed. No specific tests were performed to assess the urine excretion of methyl aminolevulinate and its derived compounds.

MICROBIOLOGY

Not Applicable

TOXICOLOGY

Special Tolerance Studies in Humans

A cumulative irritancy and sensitization study of METVIX cream was performed in 25 healthy subjects. Signs of mild to moderate skin irritancy were seen in 12 subjects after 4 days of continuous exposure. Challenge applications at previously untested sites following a two-week induction period, resulted in 5 subjects with contact sensitization.

A second cumulative irritancy and sensitization (allergenicity) study of METVIX cream with a cross-sensitization challenge with aminolevulinic acid (ALA) was performed in 156 healthy subjects. METVIX cream was applied 3 times each week for 3 weeks (total of 9 applications), to separate sites on the back of healthy volunteers. After each application, the area was covered by an aluminum Finn Chamber. After the 3-week continuous treatment period and a 2-week interval without further applications, subjects were challenged with METVIX cream, METVIX vehicle, ALA, and ALA-vehicle creams for 48 hours. Assessment of skin reactions was performed 48, 72, and 96 h after start of the challenge cream application. Only 98 of the 156 subjects tested entered the challenge phase because of a high incidence of local irritancy evident as erythema. Of the 58 subjects who were challenged with METVIX cream, 30 (52 %) showed contact sensitization. Of the

98 subjects who were challenged with ALA, only 2 (2 %) showed equivocal reactions, the remaining subjects having negative responses.

The potential for sensitization was also assessed by patch testing a total of 21 patients with actinic keratoses previously treated with METVIX-PDT on at least 4 previous occasions. METVIX cream 168 mg/g and vehicle cream were applied to different sites on the lower back for 48 hours. Three of the 21 patients (14%) showed contact sensitization associated with erythema scores ≥ 4 (strong erythema spreading outside the patch) and edema, vesiculation, papules and glazing.

These artificially intense conditions are not representative of clinical exposure and to date there have been no cases of contact sensitization in clinical trials and only a few cases in post- marketing surveillance (see Adverse Reactions).

Animal Toxicity Studies

Single-dose Toxicity: Single dose toxicity studies with rats and mice have been performed using two alternative administration routes (Table 3-1). No particular toxicity was observed after oral administration of 2000 mg/kg. With intravenous administration, it was established that the acute minimum lethal dose level of methyl aminolevulinate in the mouse and in the rat were at approximately 925 mg/kg and 1430 - 1500 mg/kg, respectively.

Table 3-1: Single-dose toxicity studies

Species	Route of Administration	Dosage Form (Vehicle)	Doses (mg/kg)	No. of animals dosed & Gender
Mouse	Oral gavage	Cream (Purified water)	2000	1M, 1F (prelimary) 5M, 5F (main study)
Rat	Oral gavage	Cream (Purified water)	2000	2F (prelimary) 5M, 5F (main study)
Mouse	IV	Cream (Physiological saline)	585 700 840 925 1000 2000	2M 2M 2M 5M 1M 1M, 1F
Rat	IV	Cream (Physiological saline)	1000 1200 1430 1500 (main study) 2000	1M 2M 2M 5M 1M, 1F

Multi-dose Toxicity: Multi-dose toxicity studies performed in the rat are shown in Table 3-2. The No Observable Effect Level (NOEL) was >250 mg/kg in the 7-day study and 200 mg/kg in the 14-day study.

Table 3-2: Multi-dose toxicity studies

Species	Route of Administration; Dosing regimen	Dosage Form (Vehicle)	Doses (mg/kg/day)	No. of animals dosed & Gender
Rat	IV; Daily for 7 consecutive days	Cream (Physiological saline)	250 750	3M, 3F 3M, 3F
Rat	IV; Daily for 14 consecutive days	Cream (Physiological saline)	50 200 800/600*	10M, 10F 10M, 10F 10M, 10F

* Dose level reduced from 800 to 600 mg/kg/day, from Day 3 onwards, following detection of marked clinical signs of toxicity and death of one male in this group on Day 2.

There were no deaths in the 7-day study. Clinical signs were limited to red/brown staining of the nose and mouth. Clinical pathology revealed reduced blood cell counts, haemoglobin, PCV, and increased lymphocyte and WBC counts among males. Bilirubin levels were elevated in both males and females. No notable macroscopic abnormalities were observed.

In the 14-day study, one male rat died following two doses of 800 mg/kg. Clinical signs in the high-dose group, immediately after dosing, included ataxias, salivation, and noisy respiration. Also observed were increased bilirubin, alanine transferase, and reduced alkaline phosphatase. Dose-related increase in liver weight was manifested in both sexes. The liver is clearly a target organ for toxicity. The observed cholangitis/pericholangitis indicates secretion into the bile duct of the compound or its metabolites.

Genotoxicity: Methyl aminolevulinate had no genotoxic effects in the Ames assay, with and without metabolic activation. Methyl aminolevulinate did not induce chromosomal aberrations in Chinese hamster ovary cells, in the presence or absence of light. Methyl aminolevulinate was also negative in the *in vivo* micronucleus assay in the rat.

There was evidence of cytotoxicity in the observed trend toward dose-related reduction in cell number. In addition, phototoxic effects were observed at higher light doses. The role of photoactivation in the micronucleus test could not be investigated due to inaccessibility of the rat femur to photoactivating light. In the *in vivo* micronucleus study, there were no clinical signs at 250 mg/kg/day; however, the following signs emerged at the 500 and 1000 mg/kg/day doses: irregular breathing, pilo-erection, and unsteady gait. At the 1000 mg/kg/day dose, prostration, convulsion, protruding eyes, salivation, eye secretion, and hunched posture were also noted.

Table 3-3: Genotoxicity studies

Type of Study	Method of Administration; Dosing Regimen	Dosage Form (Vehicle)	Dose
Ames Test	In vitro; single- dose	Cream (Purified water)	In µg/plate: 8 to 5000
Ames Test	In vitro with light activation; single-dose	Cream (Purified water)	In µg/plate: 5 to 5000
Chromosome aberration using CHO cells	In vitro with light activation; single-dose	Cream (Purified water)	In µg/mL: 24.45 to 1816
Induction of micronuclei	IV; Daily for 2 consecutive days	Cream (Purified water)	In mg/kg: 250 500 1000

Local Tolerance: In the local tolerance studies shown in Table 3-4, there was no indication of systemic toxicity after single or repeated dermal application of methyl aminolevulinate cream. There were no unexpected findings after investigation of the nature of the local lesions both macroscopically and by histopathology after single or repeated dermal treatment. In addition, the skin lesions appeared to heal after repeated treatments.

Pharmacokinetic samplings and analyses have shown no systemic exposure after single treatment, but possible systemic exposure after four successive repeated dermal applications. The eye irritation study results showed that accidental eye exposure does not cause severe adverse effects.

Table 3-4: Local tolerance studies

Species	Method of Administration; Dosing Regimen	Dose (% P- 1202* in cream)	Exposure time (h)	Photo-activation (J/cm2)	No. of animals dosed & Gender
Rat	Topical with light activation; Single-dose	20 20 2 20	12 12 12 36	100 200 100 100	11M, 11F 11M, 11F 11M, 11F 11M, 11F
Rat	Topical with light activation; Four repeated doses	20 2 10 20	24 24 24 24	0 100 100 100	10M, 10F 10M, 10F 10M, 10F 10M, 10F
Minipig	Topical with light activation; Four repeated doses	20	3	75 75	4M, 4F 4M, 4F
Rabbit	Ocular; single-dose	~7 mg/kg	-		2M, 1F 3M 2M, 1F

*P-1202 is methyl 5-aminolevulinate hydrochloride

Skin Sensitization Study: Intradermal injection of 10-60% w/v methyl aminolevulinate cream elicited a positive response, indicative of skin sensitization (delayed contact hypersensitivity) in 13 of the 20 guinea pigs tested.

Carcinogenic or Cocarcinogenic Potential: Long-term studies to evaluate the carcinogenic potential of methyl aminolevulinate have not been performed.

Reproductive Toxicity: A Maximum Topical Human Dose (MTHD) of 2 g of METVIX cream (168 mg/g methyl aminolevulinate) containing 420 mg methyl aminolevulinate hydrochloride corresponding to 7 mg/kg or 259 mg/m^2 for a 60 kg patient and an estimated maximum systemic uptake of 1% was used for the animal multiple of human systemic exposure calculations presented in this labelling.

A fertility study was performed in male and female rats with intravenous doses of methyl aminolevulinate up to 500 mg/kg/day (3000 mg/m^2, 1158 times the MTHD). Males were treated for 4 weeks prior to mating and for 5 additional weeks after mating. The females were treated for 2 weeks prior to mating and then until Day 6 of gestation. There were no treatment- related effects on fertility and mating performance seen in this study.

Development toxicity studies have been performed in pregnant rats with intravenous doses of methyl aminolevulinate up to 700 mg/kg/day on Days 6 to 16 of gestation. There were no treatment-related effects on fetal body weight, sex ratio, external malformations and variations, and skeletal abnormalities and ossification extent. Only a slight, non-significant increase in early embryonic death was noted in the 700 mg/kg/day group, compared to the control group. The fetal NOAEL (No Adverse Effect Level) was 350 mg/kg/day methyl aminolevulinate in pregnant rats (2100 mg/m^2, 811 times the MTHD based on mg/m^2 comparisons and an estimated maximum systemic uptake of 1%).

Development toxicity studies have also been performed in pregnant rabbits with intravenous doses of methyl aminolevulinate up to 200 mg/kg/day on Days 6 to 18 of gestation. Slightly lower fetal body weights and increased incidences of fetuses with jugals connected/fused to maxilla, supernumerary ribs, incompletely ossified cranial bones and other ossification irregularities were noted in the high dose (200 mg/kg/day) group, compared to the control group. The fetal NOAEL was 100 mg/kg/day methyl aminolevulinate in pregnant rabbits (1200 mg/m^2, 463 times the MTHD based on mg/m^2 comparisons and an estimated maximum systemic uptake of 1%).

In the prenatal and postnatal development toxicity study in rats treated with intravenous doses of methyl aminolevulinate up to 500 mg/kg/day from Day 6 of gestation to Day 24 of lactation, there were no treatment-related effects on litter size, pup mortality, pup weights, and post weaning performance of the F1 animals including development and reproductive capacity. Only a slightly longer duration of gestation was noted in the 250 and 500 mg/kg/day groups. The NOAEL was 125 mg/kg/day methyl aminolevulinate hydrochloride (750 mg/m^2, 290 times the MTHD based on mg/m^2 comparisons and an estimated maximum systemic uptake of 1%).

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PART III: CONSUMER INFORMATION

PrMETVIX®
methyl aminolevulinate
(as methyl aminolevulinate hydrochloride)
168 mg/g
Topical cream

This leaflet is part III of a three-part "Product Monograph" published when METVIX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about METVIX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
METVIX cream is a prescription cream used with light therapy to treat:
- skin growths on the face and scalp called actinic keratosis (AK). METVIX cream is only used for AK skin growths that are thin and not dark coloured. AK skin growths are pre-cancerous.
- primary superficial basal cell carcinoma (a skin cancer). METVIX cream is NOT used for lesions on the facial H-zone, e.g., ears, nose, upper lip, eyes and temples.

METVIX cream is used with light therapy either with a red light-emitting diode (LED) light source (for AK and skin cancer) or daylight (for AK only).

What it does:
The active ingredient in METVIX cream, methyl aminolevulinate is a light sensitive agent. After application of METVIX cream to the skin, it accumulates in the lesions.

When the skin lesions are exposed to light (photodynamic therapy), the light causes the drug to react with oxygen, which forms a chemical that kills the precancerous and cancer cells.

When it should not be used:
Do not use METVIX cream if:
- you are allergic to methyl aminolevulinate or to any of the ingredients in METVIX or porphyrins
- you are allergic to peanut and almond oil. METVIX contains peanut and almond oil
- you have skin photosensitivity or porphyria
- you have morpheaform basal cell cancer (a type of basal cell cancer)

What the medicinal ingredient is:
methyl aminolevulinate hydrochloride

What the nonmedicinal ingredients are:
Glyceryl monostearate, cetostearyl alcohol, polyoxyl stearate, cholesterol, oleyl alcohol, glycerol, white soft paraffin, isopropyl myristate, arachis (peanut) oil, refined almond oil, edetate disodium, methylparaben, propylparaben and purified water.

What dosage forms it comes in:
METVIX cream, 168 mg/g methyl aminolevulinate (as methyl aminolevulinate hydrochloride), is available as a 2 gram aluminum tube.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **The treatment using METVIX cream with light therapy must be provided to you by a doctor who is trained in its use.**
- **Do not get METVIX cream in your eyes or mucous membranes.**
- **Patients with superficial basal cell carcinoma must have regular follow-up of their treatment site.**
- **The long-term efficacy of METVIX for the treatment of superficial basal cell carcinoma has not been established.**

BEFORE you receive treatment with METVIX cream talk to your doctor or pharmacist if:

- you are pregnant or planning to become pregnant. It is not known if METVIX cream can harm your unborn baby.
- you are breastfeeding. Many drugs are excreted in human milk. It is not known if METVIX cream passes into your milk and if it can harm your baby.
- you are allergic to nuts or peanuts.
- you have or had skin cancer or other skin growths on your body.
- you have bleeding problems since patients with these problems were not studied.
- you have high blood pressure. Pain associated with METVIX treatment may increase your blood pressure.
- you are receiving ultraviolet (UV) therapy (e.g., tanning beds, phototherapy for another skin disorder).

<u>METVIX Using a Red LED Light Source (for AK or skin cancer)</u>
After METVIX is applied, you must have a special bandage to protect the area for the 3 hours before light therapy. Avoid exposure of the area to natural or artificial light and protect from cold temperatures. After the light therapy, the treated areas should be covered and protected from natural or artificial sunlight for at least 48 hours.

If you are unable to receive the light treatment after METVIX is applied, your healthcare professional will rinse the area to remove the cream. Protect the area where METVIX was applied from natural and artificial light for at least 48 hours.

<u>METVIX Using Daylight (for AK only)</u>
If you are being treated for AK, your doctor may choose to use METVIX with daylight. METVIX with daylight treatment can be used if the temperature is suitable to stay comfortably outdoors for 2 hours (usually when the temperature is above 10°C and below 35°C). If it is raining or snowing, or if it looks like it will rain or snow, METVIX daylight treatment should not be used. Daylight may not be sufficient for METVIX daylight treatment from November to March.

If you are unable to go outside as planned after you leave the doctor's office, you should wash the METVIX cream off with soap and water. Protect the area where METVIX was applied from natural and artificial light for at least 48 hours.

INTERACTIONS WITH THIS MEDICATION

It is not known if METVIX cream and other medicines can affect each other. It is possible that other light sensitive drugs when used at the same time as METVIX cream will increase some of the side effects of METVIX cream, mainly skin reactions when exposed to light (photosensitivity). Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Interactions with cosmetics, such as soaps and moisturizers, and sunscreens have not been studied.

PROPER USE OF THIS MEDICATION

Usual Dose:

METVIX Using a Red LED Light Source (for AK or skin cancer)
For skin cancer, the treatment consists of 2 treatment sessions; each session is 7 days apart.

For AK, the treatment consists of 1 treatment session.

Each treatment consists of the following steps:
1. Lesion debriding – the lesion (affected area) is scraped with a small dermal curette to remove crusts and scales.
2. METVIX cream application – METVIX cream is applied to the lesion.
3. Bandage application – the lesion is covered with a special bandage for 3 hours. Avoid exposure of the treated area to natural or artificial light and protect from cold temperatures.
4. Cream removal – the special bandage is removed and the treated area is rinsed with saline solution to remove METVIX cream.
5. Red LED light therapy – the lesion is treated with a red light for about 10 minutes; goggles should be worn to protect the eyes.

More than one lesion can be treated at a time and a maximum of 2 grams of METVIX can be used per session.

Your doctor will need to see you after 3 months to determine if the treatment worked for you.

At the 3-month check-up, a second 2 treatment sessions (for skin cancer), or 1 treatment session (for AK), of the lesion may be considered if needed.

METVIX Using Daylight (for AK only)
You will receive one treatment with METVIX using daylight.

METVIX daylight treatment can be used if the temperature conditions are suitable for you to stay comfortably outdoors for 2 hours (more than 10°C and less than 35°C). If it is raining or snowing, or if it looks like it will rain or snow, METVIX daylight treatment should not be used.

Each treatment with METVIX using daylight consists of the following steps:
1. Sunscreen application: Sunscreen is applied to all sun exposed areas, including the treatment areas. The sunscreen used must offer protection from the sun (SPF30 or higher) and should not include physical filters like titanium dioxide, zinc oxide or iron oxide. Only sunscreens with chemical filters should be used. Your doctor will tell you what sunscreen to use.
2. Lesion debriding: Once sunscreen has dried, the lesion (affected area) is scraped with a small dermal curette to remove crusts and scales.
3. METVIX cream application: METVIX cream is applied to the lesion. The treated area should be left uncovered.
4. Daylight therapy: You should go outside right after METVIX application or no later than 30 minutes after application. Once outside, you must stay outdoors for 2 continuous hours in full daylight and avoid going indoors. On sunny days, if you are uncomfortable in direct sunlight, you may go in the shade. Make sure the treatment area is continuously exposed to daylight, and not covered by clothes. It is important to follow these instructions to ensure treatment success and avoid pain during daylight exposure.
5. METVIX cream removal: Once you have been outdoors for 2 hours, you will need to wash the METVIX cream off with soap and water.

More than one lesion can be treated at a time and a maximum of 2 grams of METVIX can be used per session.

Your doctor will need to see you after 3 months to determine if the treatment worked for you. At the 3-month check-up, a second treatment session of the lesion may be considered if needed.

Overdose:
METVIX cream overdose has not been reported. There is no information on overdose of light following METVIX cream application.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss any session of your scheduled treatment, or any step of each treatment session, contact your doctor's office for advice.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The majority of side effects are self-limiting reactions at the lesion site, which occur during and immediately after light therapy, and do not require treatment. Very common side effects of METVIX cream with photodynamic therapy with red LED light treatment include the following skin reactions at the treated site:

- burning feeling
- redness
- pain
- stinging
- swelling
- crusting, peeling, blisters, bleeding, itching, ulcers
- infection

The side effects for METVIX using daylight are similar to those seen with METVIX using red LED light. However, there is less pain and skin discomfort with METVIX using daylight compared to Metvix using red LED light.

Tell your doctor if you get any of these side effects. Your healthcare provider should be able to offer advice on how to treat these reactions according to standard treatments for such skin reactions.

These reactions usually go away within 10 days of treatment. Redness may last for up to 1 month. If any of your skin reactions get worse, become severe, or last longer than 3 weeks, call your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor	
		Only if severe	In all cases
Common	skin discomfort	✓	
	redness	✓	
	skin peeling	✓	
	headache	✓	
Uncommon	scabbing	✓	
	blister	✓	
	skin swelling	✓	
	eyelid swelling	✓	
	face swelling	✓	
	tightness of throat		✓

This is not a complete list of side effects. For any unexpected effects while taking METVIX, contact your doctor or pharmacist.

HOW TO STORE IT

Store refrigerated 2-8°C (36-46°F).

Use contents within 3 months after opening.

Should not be used after 24 hours without refrigeration.

Keep out of reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
https://www.galderma.com/canada
or by contacting the sponsor, Galderma Canada Inc., at: 1-800-467-2081
This leaflet was prepared by Galderma Canada Inc.

Last revised: Sep. 09, 2022