

## PRODUCT MONOGRAPH

**Pr METVIX™**

methyl aminolevulinate topical cream  
168 mg/g  
(as methyl aminolevulinate hydrochloride)

Anti-neoplastic Agent

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# METVIX™

methyl aminolevulinate topical cream

## 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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

Metvix™ cream in combination with 630 nm wavelength red light illumination using the Aktelite CL 128 lamp 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.

This product should be administered in the physician's office by a trained physician only. Care should be taken by the physician when applying Metvix cream to avoid inadvertent skin contact (see Warnings and Precautions).

**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.
- This product should be administered by trained physicians only.
- Care should be taken by the physician when applying Metvix cream to avoid inadvertent skin contact (see Sensitivity/Resistance section below).
- Patients with sBCC treated with Metvix-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-PDT with Aktelite CL128 for the treatment of sBCC has not been established. Data from studies performed with a different lamp showed that the sBCC lesion CR at 12 months was similar to that observed with the Aktelite CL128 lamp, but decreased to 29-60% at 60 months post-treatment.

### General

**Metvix Cream Application:** 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, the 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:** 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.

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.

### **Carcinogenesis and Mutagenesis**

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

### **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**

Contact sensitization (allergenicity) has been observed in 14-52% of subjects previously exposed to Metvix on at least 4 occasions (See Toxicology). Care should be taken by the physician 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.

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.

### **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, caution should be exercised when Metvix is administered to a nursing woman.

**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.

### **Clinical Trial Adverse Drug Reactions**

**Actinic Keratosis Studies:** A total of 231 subjects, each with 4 - 10 actinic keratoses were enrolled in 2 double-blind, randomized, vehicle-controlled clinical trials. Subjects were randomized to receive Aktelite 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 Aktelite CL128 lamp, delivering red light at a dose of 37 J/cm<sup>2</sup>.

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  $\geq 1\%$  of Subjects with actinic keratoses in Studies 1 and 2 (Safety Population)**

	Metvix & Aktelite PDT n = 126		Vehicle & Aktelite PDT n = 105	
	All Events*	Severe	All Events*	Severe
<b>Any Treatment Site Adverse Drug Reaction</b>	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%)
<b>Non Treatment Site Adverse Drug Reaction</b>	13 (10%)	2 (2%)	0 (0%)	0 (0%)
Headache	3 (2%)	1 (1%)	0 (0%)	0 (0%)

\*Mild, Moderate, or Severe

The most common adverse drug reactions were attributable to phototoxicity reactions at the treatment site.

**Less Common Clinical Trial Adverse Drug Reactions in Actinic Keratoses Studies (<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

**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-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-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 1-2.

**Table 1-2: 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
<b>ANY ADVERSE EVENT</b>		<b>26 (26.0%)</b>	<b>11 (11%)</b>	<b>10 (10.4%)</b>	<b>3 (3.1%)</b>	<b>1 (1.0%)</b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	Pain	1 (1%)	1 (1%)	-	-	1 (1.0%)
<b>INFECTIONS AND INFESTATIONS</b>	<b>ALL</b>	<b>1 (1%)</b>	-	<b>3 (3.1%)</b>	<b>1 (1.0%)</b>	<b>1 (1.0%)</b>
	Application site infection	1 (1%)	-	-	-	-
	Wound infection	-	-	3 (3.1%)	1 (1.0%)	1 (1.0%)
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</b>	Basal cell carcinoma	-	1 (1%)	-	-	-
<b>NERVOUS SYSTEM DISORDERS</b>	Headache	1 (1%)	-	-	-	-
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	<b>ALL</b>	<b>24 (24%)</b>	<b>9 (9%)</b>	<b>5 (5.2%)</b>	<b>1 (1.0%)</b>	-
	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%)	-	-
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>ALL</b>	-	-	<b>4 (4.2%)</b>	<b>1 (1.0%)</b>	-
	Post procedural pain	-	-	2 (2.1%)	1 (1.0%)	-
	Wound dehiscence	-	-	2 (2.1%)	-	-
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	Shoulder pain	-	-	1 (1.0%)	-	-
<b>SURGICAL AND MEDICAL PROCEDURES</b>	<b>ALL</b>	-	-	<b>2 (2.1%)</b>	-	-
	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-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-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 parathesia, and, urticaria, rash, skin hypopigmentation, heat rash, and fatigue in Phase III studies in which the illumination 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 and urticaria have been described in post-marketing reports. Most cases were localized to the treatment area and were not severe; some cases of erythema and swelling have been more extensive.

## **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.

## **Recommended Dose and Dosage Adjustment**

**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 should be performed followed by a second treatment session 7 days later. The treated lesions should be evaluated after 3 months, and up to two additional treatment sessions can be performed if needed. Multiple lesions can be treated in one session. Metvix-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-PDT 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.

### **Missed Dose**

If the patient for any reason cannot have the red light treatment within the 3 hour prescribed period after 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**

One Metvix-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

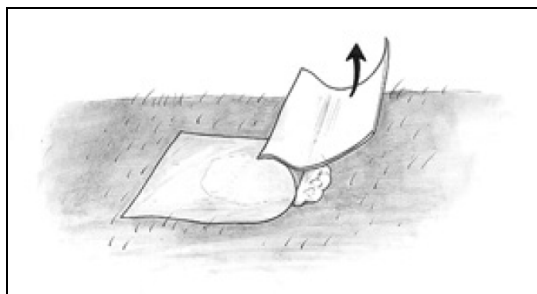
Only nitrile gloves should be worn during this and subsequent steps and universal precautions should be taken. Vinyl and latex gloves do not provide adequate protection when using this product.

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



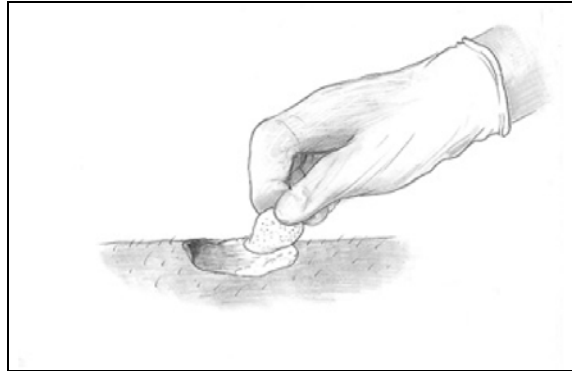
## 4) Wait for 3 hours (at least 2.5 hours, but no more than 4 hours) (see Warnings and Precautions)

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). Nitrile gloves should be worn.

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  $200 \text{ mW/cm}^2$ . 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  $630 \text{ nm}$  and a total light dose of  $37 \text{ J/cm}^2$  (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. Use of Metvix cream without subsequent red light illumination is not recommended.

## 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<sup>2</sup>, is the basis for Metvix photodynamic therapy (PDT).

### 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<sup>2</sup> 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 °C.

Shelf-life: 18 months.

Use contents within one week 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

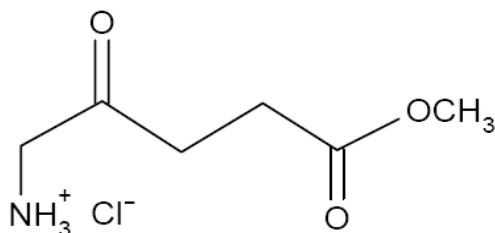
#### Drug Substance

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 and molecular mass:  $C_6H_{11}NO_3 \cdot HCl$  181.62

Structural formula:



Physicochemical properties: Methyl aminolevulinate hydrochloride is a white to slightly yellow 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

#### A. ACTINIC KERATOSIS

Two pivotal multicenter, double-blind, randomized, vehicle-controlled, parallel group Phase III studies (PC T404/05 and PC T405/05) involving 106 patients with 781 actinic keratosis lesions (with a median of 7 lesions per patient) treated with Metvix-PDT were performed, in which the efficacy and safety of Metvix-PDT using the Aktelite CL128 lamp were studied.

Before administration of Metvix cream or vehicle cream, the lesion was prepared to facilitate application of cream and access of light to all parts of the lesion. Scales and crusts were removed

with a small dermal curette and the surface of the lesion was gently scraped in order to roughen the surface.

For all the lesions, a thick (approximately 1 mm) layer of study cream was applied directly to the lesion and on 5 mm of surrounding tissue, either with a spatula or by pressing the dressing down over the cream. The amount of cream that was used depended on the size of the lesion. An occlusive dressing was used to cover the area of study cream application. The dressing edges were smoothed down to ensure that the dressing was fixed. When the cream had been in place for 3 hours, the dressing was removed and the study cream was gently wiped off.

The treated skin area was illuminated with a 630 nm red light at the recommended dose of 37 J/cm<sup>2</sup> (Aktilite CL128). A second treatment session was performed 7 days later.

## ***1. 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-PDT for the treatment of actinic keratosis. A total of 211 randomized subjects with a total of 1555 non-hyperkeratotic actinic keratoses were studied. 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 -PDT  n = 49	Vehicle -PDT  n = 47	Total  n = 96	Metvix -PDT  n = 57	Vehicle -PDT  n = 58	Total  n = 115	Metvix -PDT  n = 106	Vehicle -PDT  n = 105	Total  n = 211
<b>Gender n (%)</b>									
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)
<b>Age (y)</b>									
<b>Mean (SD)</b>	66.1 (10.2)	66.7 (9.2)	66.4 (9.7)	69.5 (9.0)	67.0 (10.4)	68.2 (9.8)	67.9 (9.7)	66.8 (9.8)	67.4 (9.7)
<b>Range</b>	43 – 86	48 – 89	43 – 89	47 – 88	41 – 90	41 – 90	43 – 88	41 – 90	41 – 90
<b>Number (%) of patients aged ≤65 and ≥65 years</b>									
≤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)
<b>Number (%) of patients with each skin type</b>									
<b>I</b>	12 (24)	10 (21)	22 (23)	10 (18)	12 (21)	22 (19)	22 (21)	22 (21)	44 (21)
<b>II</b>	22 (45)	26 (55)	48 (50)	28 (49)	23 (40)	51 (44)	50 (47)	49 (47)	99 (47)
<b>III</b>	12 (24)	10 (21)	22 (23)	13 (23)	18 (31)	31 (27)	25 (24)	28 (27)	53 (25)
<b>IV</b>	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-PDT n = 49	Vehicle-PDT n = 47	Metvix-PDT n = 57	Vehicle-PDT n = 58
<b>Subjects with Complete Response</b>	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-PDT n = 363	Vehicle-PDT n = 360	Metvix-PDT n = 418	Vehicle-PDT n = 414
<b>Lesions with Complete Response</b>		313 (86%) <sup>†</sup>	188 (52%)	348 (83%) <sup>†</sup>	119 (29%)
<b>Grade 1</b>		<b>259</b>	<b>267</b>	<b>182*</b>	<b>161</b>
<b>Face</b>	Total	191	201	99	88
	CR	167 (87%)	121 (60%)	90 (91%)	33 (38%)
<b>Scalp</b>	Total	68	66	76	73
	CR	63 (93%)	29 (44%)	66 (87%)	31 (42%)
<b>Grade 2</b>		<b>104</b>	<b>93</b>	<b>236*</b>	<b>253</b>
<b>Face</b>	Total	76	68	119	157
	CR	65 (86%)	29 (43%)	103 (87%)	35 (22%)
<b>Scalp</b>	Total	28	25	115	96
	CR	18 (64%)	9 (36%)	89 (77%)	20 (21%)

<sup>†</sup> 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-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-PDT were 86 % and 75 % respectively.

## 2. Active-Controlled Studies

Although active-controlled studies were performed, they were primarily designed to collect safety data. Thus, no efficacy data is presented for active-controlled studies.

### B. SUPERFICIAL BASAL CELL CARCINOMA

#### 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-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-PDT and 96 to excision surgery. There were no notable differences

between the treatment groups with respect to demographic characteristics (see Table 2-4). 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-PDT and 86 subjects randomized to excision surgery.

**Table 2-4: Patient Demographic Data for Superficial Basal Cell Carcinoma Study (ITT)**

		<b>Metvix</b>	<b>Surgery</b>	<b>TOTAL</b>
<b>Gender</b>	<b>N</b>	100 (100%)	96 (100%)	196 (100%)
	<b>Male</b>	64 (64.0%)	66 (68.8%)	130 (66.3%)
	<b>Female</b>	36 (36.0%)	30 (31.3%)	66 (33.7%)
<b>Age (in Years)</b>	<b>N</b>	100	96	196
	<b>Mean ± STD</b>	64.5±12.7	63.1±13.9	63.8±13.3
	<b>Median</b>	68.5	66.5	67
	<b>(Min, Max)</b>	(33,85)	(31,92)	(31,92)
<b>Race</b>	<b>N</b>	100 (100%)	96 (100%)	196 (100%)
	<b>Caucasian</b>	100 (100.0%)	96 (100.0%)	196 (100.0%)
<b>Lesion Diameter (mm)</b>	<b>N</b>	100	94	
	<b>Mean±sd</b>	12.5 ± 3.7	12.6 ± 3.7	
<b>Number of lesions per patient</b>	<b>N</b>	100	96	
	<b>Median</b>	1.0	1.0	
<b>Lesion Distribution</b>	<b>01</b>	79 (79%)	77 (80.2%)	
	<b>02</b>	11 (11%)	8 (8.3%)	
	<b>03</b>	7 (7%)	7 (7.3%)	
	<b>04</b>	2 (2%)	2 (2.1%)	
	<b>05</b>	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-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 2-5.

**Table 2-5: Reduction in Lesion Count per subject of Metvix-PDT compared with Surgery 3 months after last treatment**

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

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-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-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-PDT group was superior to that of the surgery group (p<0.001). Please see Table 2-6 for details. Twelve months after last treatment, the investigator assessed cosmetic outcome was superior for the Metvix-PDT group compared to that of the surgery group (p<0.001), i.e., 92.8% of the subjects were considered success in Metvix-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-PDT versus 18.8% with surgery. No poor cosmetic outcomes were observed in Metvix- PDT group whereas 5 (4.8%) were rated as poor for the surgery group.

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

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

(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 dose. 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<sup>2</sup> 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<sup>2</sup> 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**

### **A. 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  $\geq 4$  (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).

## **B. 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 (preliminary) 5M, 5F (main study)
Rat	Oral gavage	Cream (Purified water)	2000	2F (preliminary) 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	<i>In vitro</i> ; single-dose	Cream (Purified water)	<u>In µg/plate:</u> <u>8 to 5000</u>
Ames Test	<i>In vitro</i> with light activation; single-dose	Cream (Purified water)	<u>In µg/plate:</u> <u>5 to 5000</u>
Chromosome aberration using CHO cells	<i>In vitro</i> with light activation; single-dose	Cream (Purified water)	<u>In µg/mL:</u> <u>24.45 to 1816</u>
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/cm <sup>2</sup> )	No. of animals dosed & Gender
Rat	Topical with light activation; Single-dose	20	<u>12</u>	100	11M, 11F
		20	<u>12</u>	200	11M, 11F
		2	<u>12</u>	100	11M, 11F
		20	<u>36</u>	100	11M, 11F
Rat	Topical with light activation; Four repeated doses	20	24	0	10M, 10F
		2	24	100	10M, 10F
		10	24	100	10M, 10F
		20	24	100	10M, 10F
Minipig	Topical with light activation; Four repeated doses	20	3	75	4M, 4F
				75	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<sup>2</sup> 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<sup>2</sup>, 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<sup>2</sup>, 811 times the MTHD based on mg/m<sup>2</sup> 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<sup>2</sup>, 463 times the MTHD based on mg/m<sup>2</sup> 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<sup>2</sup>, 290 times the MTHD based on mg/m<sup>2</sup> comparisons and an estimated maximum systemic uptake of 1%).

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## PART III: CONSUMER INFORMATION

**METVIX™**  
methyl aminolevulinate 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 photodynamic therapy (PDT or red light treatment) 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 not 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.

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 important 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 and light therapy must be provided to you by a doctor who is trained in their 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

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, rinse the area to remove the cream, and protect it from natural and artificial light for at least 48 hours. You must wear special Nitrile gloves when you remove the cream.

**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:

The treatment consists of 2 treatment sessions; each session is 7 days apart. Each treatment consists of the following steps:

1. Lesion debriding – the lesion (affected area) is scraped 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. Light therapy (photodynamic therapy or PDT) – 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 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.

### 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 treatment include the following skin reactions at the treated site:

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

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	T	
	redness	T	
	skin peeling	T	
	headache	T	
Uncommon	scabbing	T	
	blister	T	
	skin swelling	T	
	eyelid swelling	T	

*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 one week after opening.

Should not be used after 24 hours without refrigeration.

Shelf-life: 18 months.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

toll-free telephone: 866-234-2345  
toll-free fax 866-678-6789  
By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:  
Canada Vigilance National Office  
Marketed Health Products Safety and Effectiveness  
Information Bureau  
Marketed Health Products Directorate  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance.  
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:

<http://www.galderma.ca>

or by contacting the sponsor, Galderma Canada Inc., at:  
1-800-467-2081

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