PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**UVADEX®**

Methoxsalen

Sterile Solution, 20 mcg/mL, for extracorporeal administration

Antineoplastic Agent, ATC code: D05BA02

For use with the THERAKOS® CELLEX® Photopheresis System

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General, Driving and Operating Machinery, Carcinogenicity and Mutagenesis	08/2021
7 WARNINGS AND PRECAUTIONS, General, Carcinogenicity and Mutagenesis	08/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the THERAKOS® CELLEX® Photopheresis System in the palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL) that is unresponsive to other forms of treatment.

The indication was authorized based on response rate (25% reduction in skin score maintained for four consecutive weeks) demonstrated in a single-arm phase II study (see 14 CLINICAL TRIALS).

Only patients with patch plaque, extensive plaque and erythrodermic disease were enrolled in these studies.

There are no data available regarding the efficacy of UVADEX in patients with disease in the tumor phase.

There is no clinical evidence to show that treatment with UVADEX beyond six months provides additional benefit if the patient has not responded within this timeframe (see 14 CLINICAL TRIALS).

1.1 Pediatrics

- Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- UVADEX is contraindicated in patients who are hypersensitive to this drug or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients possessing a specific history of a light sensitive disease state should not initiate methoxsalen therapy. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum and albinism.
- UVADEX is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses.
- UVADEX is contraindicated in patients with severe cardiac disease, severe anemia, white blood cell count greater than 25,000 mm^3, previous splenectomy and coagulation disorders.

- UVADEX is contraindicated in patients with co-existing melanoma, basal cell, or squamous cell skin carcinoma.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Carcinogenicity (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY)
- Mutagenicity (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY)
- Teratogenicity (see 7 WARNINGS AND PRECAUTIONS and 7.1.1 Pregnant Women)
- Cataractogenicity (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic)
- Skin burning (see 7 WARNINGS AND PRECAUTIONS, Skin)

4 DOSAGE AND ADMINISTRATION

UVADEX should be administered under the supervision of a health professional experienced with treatment of cutaneous T-cell lymphoma and the use of THERAKOS CELLEX Photopheresis System.

4.1 Dosing Considerations

During treatment with the THERAKOS CELLEX Photopheresis System, the dosage of UVADEX for each treatment will be calculated according to the treatment volume.

The prescribed amount of UVADEX should be injected into the recirculation bag prior to the Photoactivation Phase using the formula:

TREATMENT VOLUME X 0.017 = mL of UVADEX for each treatment

Example: Treatment volume of 240 mL X 0.017 = 4.1 mL of UVADEX

4.2 Recommended Dose and Dosage Adjustment

Normal Treatment Schedule:

Treatment is given on two consecutive days every four weeks for a minimum of seven treatment cycles (six months).

Accelerated Treatment Schedule:

If the assessment of the patient during the fourth treatment cycle (approximately three months) reveals an increased skin score from the baseline score, the frequency of treatment may be increased to two consecutive treatments every two weeks. If a 25% improvement in the skin score is attained after four consecutive weeks, the regular treatment schedule may resume. Patients who are maintained in the accelerated treatment schedule may receive a maximum of 20 cycles. There is no clinical evidence to show that treatment with UVADEX beyond six months provides additional benefit if the patient has not responded within this timeframe or that using a different schedule provides additional benefit. In Study CTCL 3, 15 of the 17 responses were seen within six months of treatment and only two patients responded to treatment after six months.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

UVADEX is administered extracorporeally via the THERAKOS CELLEX Photopheresis System.

Read the THERAKOS CELLEX Photopheresis Operator's Manual before administering the treatment.

Do not inject directly into patients.

Each UVADEX treatment involves collection of leukocytes, photoactivation, and reinfusion of photoactivated cells. In the photopheresis process, the patient is connected to the THERAKOS CELLEX instrument via a catheter interface. Red blood cells are separated from the white blood cells and plasma in the centrifuge bowl. The red blood cells and excess plasma are returned to the patient while the buffy coat (leukocyte-enriched blood) and some plasma are collected into the photoactivation bag located on the side of the instrument.

The prescribed amount of UVADEX is injected into the recirculation bag prior to the photoactivation phase (see 11 STORAGE, STABILITY AND DISPOSAL). During photoactivation the leukocyte-enriched blood is continually circulated through the photoactivation chamber (photoceptor) while being exposed to UVA light (1.5-2 J/cm^2). At the end of the photoactivation cycle, the photoactivated cells are then reinfused into the patient.

UVADEX is supplied in 10 mL vials containing 200 mcg of methoxsalen (concentration of 20 mcg/mL). There are no preservatives or bacteriostatic agents in the vial, therefore the vial is intended for SINGLE USE ONLY.

The THERAKOS CELLEX Photopheresis System Operator's Manual should be consulted before using this product.

5 OVERDOSAGE

In the event of overdosage, the patient should be kept in a darkened room for at least 24 hours.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Extracorporeal	Solution, 20mcg/mL	Alcohol 95% 0.05 mL, glacial acetic acid 0.0012 mL, propylene glycol 50 mg, sodium acetate trihydrate 1.75 mg, sodium chloride 8 mg, water for injection q.s. to 1.0 mL. Glacial acetic acid q.s. to pH 4.5 ± 0.1 and sodium hydroxide q.s. to pH 4.5 ± 0.1 are used to adjust pH.

UVADEX is used in combination with the THERAKOS CELLEX Photopheresis System to extracorporeally treat leukocyte enriched buffy coat.

UVADEX is a clear, colorless to pale yellow liquid.

UVADEX is supplied in 10 mL vials, cartons of 12 vials.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

Carcinogenesis and Mutagenesis

Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. In a prospective study of 1380 patients given PUVA therapy for psoriasis, 237 patients developed 1422 cutaneous squamous cell cancers. This observed incidence of cutaneous carcinoma is 17.6 times that expected for the general population. Previous cutaneous exposure to tar and UVB treatment, ionizing radiation or arsenic increased the risk of developing skin carcinomas after PUVA therapy. Because the dose of methoxsalen with UVADEX therapy is about 200 times less than with PUVA and the skin is not exposed to high cumulative doses of UVA light, the risk of developing skin cancer following UVADEX therapy may be lower. Monitor patients with a history of malignant or semi-malignant skin tumors.

Methoxsalen was carcinogenic in male rats that were given the drug by oral gavage five days per week for 103 weeks at doses of 37.5 and 75 mg/kg. The 37.5 mg/kg dose is about 1900 times greater than a single human methoxsalen dose during extracorporeal photopheresis treatment on a body surface area basis. The neoplastic lesions in rats included adenomas and adenocarcinomas of the tubular epithelium of the kidneys, carcinoma or squamous cell carcinoma of the Zymbal gland and alveolar or bronchiolar adenomas. Topical or intraperitoneal methoxsalen is a potent photo-carcinogen in albino mice and hairless mice (see 16 NON-CLINICAL TOXICOLOGY).

With S9 activation, methoxsalen is mutagenic in the Ames test. In the absence of S9 activation and UV light, methoxsalen is clastogenic *in vitro* (sister chromatid exchange and chromosome aberrations in Chinese hamster ovary cells). Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair.

Concomitant Use with Other Photosensitizing Agents

Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents such as anthralin, coal tar or coal tar derivatives, griseofulvin, phenothiazines, nalidixic acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes such as methylene blue, toluidine blue, rose bengal and methyl orange.

Driving and Operating Machinery

Because of the possibility of transient cardiovascular instability and the recommendation that following photopheresis patients wear sunglasses, photopheresis treatment using UVADEX is likely to produce minor or moderate undesirable effects and patients should not drive or operate machinery immediately following photopheresis.

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hepatic/Biliary/Pancreatic

No specific information is available on the use of photopheresis using UVADEX in patients with hepatic impairment. Since hepatic biotransformation is necessary for urinary excretion, it is possible that hepatic impairment may result in an extended half-life of methoxsalen. This may lead to prolonged photosensitivity and thus require continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.

Monitoring and Laboratory Tests

In consultation with the physician, assess the patient's overall health status immediately before beginning photopheresis treatment to determine if the patient is able to tolerate the anticipated fluid shifts during the treatment with the THERAKOS Photopheresis System. Do not proceed if the patient is unstable.

The physician should review the patient's medical condition, medications and platelet count at the time of treatment and use clinical judgment to establish the optimal heparin dosage for each patient.

Ophthalmologic

Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity. The concentration of methoxsalen in the human lens is proportional to the concentration in serum. Serum methoxsalen concentrations are substantially lower after extracorporeal UVADEX treatment than after oral methoxsalen treatment. Nevertheless, if the lens is exposed to UVA light while methoxsalen is present, photoactivation of the drug may cause adducts to bind to biomolecules within the lens. If the lens is shielded from UVA light, the methoxsalen will diffuse out of the lens in about 24 hours.

Patients who use proper eye protection after PUVA therapy (oral methoxsalen) appear to have no increased risk of developing cataracts. The incidence of cataracts in these patients five years after their first treatment is about the same as that in the general population. Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after UVADEX treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.

Reproductive Health: Female and Male Potential

No data are available on the reproductive effects of UVADEX in humans.

Both men and women who are being treated with UVADEX should take adequate contraceptive precautions both during and after completion of photopheresis therapy (see 7.1.1 Pregnant Women).

- **Fertility**

  There is no animal or human data on the effects of UVADEX on fertility.

- **Teratogenic Risk**

  See 7.1.1 Pregnant Women.

Skin

After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin.

Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions not followed. Patients should cover exposed skin or use sunblock (SPF 15 or higher) for 24 hours following treatment with methoxsalen, whether exposed to direct or indirect sunlight outdoors or through a window (see 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

7.1 Special Populations

7.1.1 Pregnant Women

No pregnant women were exposed to UVADEX during clinical trials. Methoxsalen may cause fetal harm when given to a pregnant woman. Doses of 80 to 160 mg/kg/day given during organogenesis caused significant fetal toxicity in rats. The lowest of these doses, 80 mg/kg/day, is over 4000 times greater than a single dose of UVADEX on a mg/m^2 basis. Fetal toxicity was associated with significant maternal weight loss, anorexia and increased relative liver weight. Signs of fetal toxicity included increased fetal mortality, increased resorptions, late fetal death, fewer fetuses per litter, and decreased fetal weight. Methoxsalen caused an increase in skeletal malformation and variations at doses of 80 mg/kg/day and above.

There are no adequate and well-controlled studies of methoxsalen in pregnant women. If UVADEX is used during pregnancy, or if the patient becomes pregnant while receiving UVADEX, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

7.1.2 Breast-feeding

It is unknown if methoxsalen is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Safety in children has not been established. Potential hazards of

long-term therapy include the possibilities of carcinogenicity and cataractogenicity as well as the probability of actinic degeneration.

7.1.4 Geriatrics

The effect of age on the pharmacokinetics of UVADEX has not been studied.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common treatment-related adverse events in the clinical study which used UVADEX in conjunction with photopheresis in CTCL in adult patients were loss of venous access (9/51, 10%) and vasovagal spasm (3/51, 3%). Nausea and vomiting were infrequent following UVADEX/ECP treatment compared to oral methoxsalen/ECP treatment with each event reported in 1/51 patients (2%).

See 7 WARNINGS AND PRECAUTIONS.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real world use.

Adverse reaction data was based on 3 open-label, single-arm trials in patients with CTCL. Studies CTCL 1 and CTCL 2 evaluated the use of oral methoxsalen with ECP in 97 patients. Oral methoxsalen was administered at a dose of 0.6 mg/kg and treatment frequency was based on clinical response. Study CTCL 3 evaluated extracorporeal administration of UVADEX in 51 patients who had an average of 20.2 treatments, with 24 patients completing all treatments. UVADEX was administered at a dose of 200 mcg with a treatment frequency of 2 treatments on 2 consecutive days every 4 weeks, with the option of increasing the frequency to 2 treatments every 2 weeks in patients with worsening skin scores after 3 months, with follow-up of up to 12 months.

Side effects of photopheresis (UVADEX used in conjunction with the THERAKOS Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%). In Study CTCL 3, six serious cardiovascular adverse experiences were reported in five patients (5/51, 10%). Five of these six events were not related to photopheresis and did not interfere with the scheduled photopheresis treatments. One patient (1/51, 2%) with ischemic heart disease had an arrhythmia after the first day of photopheresis that was resolved the next day.

Six infections were also reported in five patients. Two of the six events were Hickman catheter infections in one patient, which did not interrupt the scheduled photopheresis. The other four infections were not related to photopheresis and did not interfere with scheduled treatments.

Adverse Events associated with the photopheresis procedure used in the treatment of CTCL in clinical trials were as follows.

Event	**CTCL 3 UVADEX**		**CTCL 1&2 Oral Methoxsalen**	
	Nº of Patients (%) N=51	**Total Nº by Treatments Nº of Treatments= 1032**	**Nº of Patients (%) N= 96**	**Total Nº by Treatments Nº of Treatments= 4319**
Hypotension	0	0	7 (7.3)	7(<0.2)
Transient Fever 6-8 hours after reinfusion of photoactivated cells	0	0	8 (8.3)	17 (<0.4)
Vascular Access Complication	9 (17.6)	10 (<0.1)	0	0
Infection	1 (2.0)	1 (<0.1)	5 (5.2)	5(<0.2)

8.3 Less Common Clinical Trial Adverse Reactions

Due to the small patient population in Study CTCL 3 (n=51), there were no less common (<1%) adverse events reported in this study.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

There were some statistically significant decreases in mean changes from baseline for some routine laboratory parameters including calcium, hematocrit, hemoglobin, potassium, platelets and red blood cells however, the magnitude of these changes was not clinically significant.

8.5 Post-Market Adverse Reactions

The most common post-marketing events reported with UVADEX/ECP treatment regardless of causality assessment were obtained from spontaneous reports, clinical studies or literature and include taste perversions, vasovagal attack/fainting/dizziness, sepsis/line sepsis, anemia, hypotension, nausea, allergic reaction and photosensitivity reaction.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Although methoxsalen has been shown to be capable of both induction and inhibition of hepatic enzymes, in man it appears to act primarily as a potent inhibitor of hepatic microsomal

oxidative metabolic processes, including, but not limited to, CYP1A2, 2A6 and 2B1. Thus, it is to be expected that interactions will occur between methoxsalen and other medicinal products whose metabolism involves the hepatic cytochrome P450 system. The clearance of caffeine and antipyrine have been shown to be markedly reduced after methoxsalen treatment. Therefore, consumption of other P450 substrates may result in an extended half-life of methoxsalen, and consequently lead to prolonged photosensitivity and thus requiring continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.

Studies have shown that methoxsalen also decreases the metabolic activation of paracetamol in animals and humans, probably as a consequence of methoxsalen associated inhibition of hepatic cytochrome P450 oxidative transformation of paracetamol. One report describes a psoriatic and epileptic patient in whom phenytoin administration induced increased metabolism of methoxsalen leading to low levels of methoxsalen and failure of PUVA therapy. Substitution of valproate for phenytoin resulted in a three to four-fold increase in methoxsalen levels to within the putative therapeutic range. In the blood methoxsalen is normally highly bound to albumin but can be displaced by a number of medicinal products such as dicoumarol, promethazine and tolbutamide. As a coumarin derivative, it is conceivable that methoxsalen binds to the warfarin site of albumin, which could be of clinical significance when the two medicinal products are coadministered. However, of the medicinal products studied, only tolbutamide at therapeutic concentrations displaces methoxsalen from its binding site to a clinically relevant extent. Concomitant use of methoxsalen and tolbutamide may therefore lead to enhanced photosensitivity. Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitising agents. Such agents include fluoroquinolones, furosemide, nalidixic acid, phenothiazines, retinoids, sulfonamides, sulfonylureas, tetracyclines, and thiazides.

9.4 Drug-Drug Interactions

See 7 WARNINGS AND PRECAUTIONS, Concomitant Use with Other Photosensitizing Agents.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Laboratory interactions have not been established.

9.8 Drug-Lifestyle Interactions

Treatment with methoxsalen may increase the skin's sensitivity to UVA light. Patients should be instructed to wear UVA-absorbing sunglasses and cover exposed skin or use a sunblock (SPF15 or higher) for 24 hours following treatment with methoxsalen, whether exposed to direct or indirect sunlight outdoors or through a window.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The exact mechanism of action of methoxsalen is not known. The best-known biochemical reaction of methoxsalen is with DNA. Methoxsalen, upon photoactivation, conjugates and forms covalent bonds with DNA which leads to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking of psoralen to both strands of DNA). Reactions with proteins have also been described.

For the palliative treatment of Cutaneous T-Cell Lymphoma, Photopheresis consists of removing a portion of the patient's blood and separating the red blood cells from the white cell layer (buffy coat) by centrifugation. The red cells are returned to the patient and UVADEX is then injected into the instrument and mixed with the buffy coat. The instrument then irradiates this drug-cell mixture with ultraviolet light (UVA light, 320-400 nm) and returns the treated cells to the patient. Animal studies suggest that the photopheresis may activate an immune-mediated response against the malignant T-cells.

10.2 Pharmacodynamics

There are no studies which have assessed the pharmacodynamics of UVADEX.

10.3 Pharmacokinetics

A study investigated the kinetics and distribution of methoxsalen following intravenous administration in 18 subjects divided into three treatment groups to receive 5, 10, and 15 mg methoxsalen infused over 60 minutes. A summary of the results is provided below.

Table – Summary of Pharmacokinetic Parameters for Intravenously Administered Methoxsalen

	C_{max} (ng/mL)	**AUC (ng•min/mL)**	**Clearance (L/kg/min)**	**MRT (min)**	**V_{ss} (L/kg)**
5 mg dose (n=6)					
Mean	60.2	4756	0.012	50.4	0.52
SD	10.4	978	0.0035	35.1	0.022
10 mg dose (n=6)					
Mean	138.7	11626	0.11	56.8	0.61
SD	33.3	3366	0.0018	16.5	0.09
15 mg dose (n=6)					
Mean	195.8	16340	0.14	58.5	0.81
SD	89.2	8474	0.0034	23.9	0.34

$C_{max:}$ maximum plasma concentration
AUC: area under the concentration over time curve
MRT: mean residence time
V_{ss}: volume of distribution at steady state

In the clinical study conducted with UVADEX, methoxsalen concentrations in plasma 30 minutes after reinfusion of the photoactivated cells were less than 10 ng/mL in 82% of the 754 samples measured. The mean plasma methoxsalen level was approximately 25 ng/mL.

In man, methoxsalen undergoes nearly complete biotransformation with little or no unchanged active substance being found in the urine or feces. Both conjugated and unconjugated metabolites have been identified. Such few data are available regarding the activity of the metabolites suggest that they do not possess the pharmacological activity of the parent compound.

In man, virtually no unchanged methoxsalen is recovered in the urine or feces following oral administration. In radiolabelled studies, at 48 hours post-dosing, urinary excretion of radioactivity averaged 74%. Biliary excretion of methoxsalen and its metabolites, as reflected by fecal recovery, was relatively minor at 14%.

The total dose of methoxsalen delivered in UVADEX is substantially lower (approximately 200 times) than that used with oral administration.

Absorption

Interpatient variability in peak plasma concentration after an oral dose of methoxsalen ranges from 6 to 15 fold. UVADEX is injected directly into the separated buffy coat in the instrument in an attempt to diminish this interpatient variability and to improve the exposure of the cells to the drug. Mean peak methoxsalen levels were reported to be <25 ng/mL in the patient and 203 ng/mL in the photoactivation bag after completion of photopheresis treatment. The total dose of methoxsalen delivered in UVADEX is substantially lower (approximately 200 times) than that used with oral administration.

Distribution

Methoxsalen is reversibly bound to serum albumin and is also preferentially taken up by epidermal cells. Methoxsalen is rapidly metabolized in humans, with approximately 95% of the drug excreted as metabolites in the urine within 24 hours.

Metabolism

The metabolism of methoxsalen has been studied in man and two animal species, the rat and dog. In man, methoxsalen undergoes nearly complete biotransformation with little or no unchanged drug being found in the urine or feces. The primary metabolic degradation involves enzymatic cleavage of the C2-C3 double bond of the furan ring but demethylation also occurs. Both conjugated and unconjugated metabolites have been identified (see 9 DRUG INTERACTIONS).

Elimination

In man, virtually no unchanged methoxsalen is recovered in the subject's urine or feces following oral administration.

Special Populations and Conditions

- **Pediatrics** The pharmacokinetics of UVADEX in patients under the age of 18 years has not been studied.
- **Geriatrics** The effect of age on the pharmacokinetics of UVADEX has not been studied.
- **Hepatic Insufficiency** No specific information is available on the use of photopheresis using UVADEX in patients with hepatic impairment. Since hepatic biotransformation is necessary for urinary excretion, it is possible that hepatic impairment may result in an extended half-life of methoxsalen. This may lead to prolonged photosensitivity and thus require continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.
- **Renal Insufficiency** There have been no studies of UVADEX in renally impaired individuals.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15-30°C.

As UVADEX can sorb onto PVC and other plastics, only the THERAKOS CELLEX photopheresis procedural kits should be used to administer this medicinal product. Typical sorption of UVADEX by plastics in the instrument's photopheresis photoactivation circuit during a photopheresis treatment is approximately 30%. Once UVADEX is drawn into a plastic syringe it should be immediately injected into the photoactivation bag.

12 SPECIAL HANDLING INSTRUCTIONS

UVADEX is intended for single-use only.

UVADEX should not be diluted. The contents of the vial should be injected into the THERAKOS CELLEX Photopheresis System immediately after being drawn up into a syringe. Do not inject directly into patients. The THERAKOS CELLEX System Operator's Manual should be consulted before using this medicinal product.

UVADEX exposed to a plastic syringe for more than one hour should be discarded.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

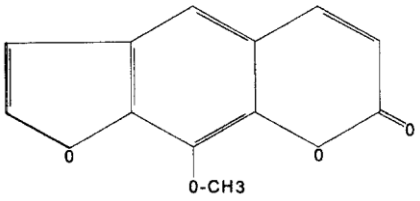
Drug Substance

Proper name: Methoxsalen

Chemical name: 9-methoxy-7H-furo{3,2-g}[1]-benzopyran-7-one

Molecular formula and molecular mass: $C_{12}H_8O_4$ 216.18

Structural formula:



Product Characteristics

Physicochemical properties: Methoxsalen drug substance appears as long white to off white needles. The crystals are odourless and have a bitter taste followed by a tingling sensation. The melting point of the crystals is 148°C. Silky needles are formed from hot water or benzene and petroleum ether. Long rhombic prisms are formed from alcohol and ether.

Methoxsalen is practically insoluble in cold water and sparingly soluble in boiling water, liquid petrolatum and ether. It is soluble in boiling alcohol, acetone, acetic acid, vegetable fixed oils, propylene glycol and benzene and freely soluble in chloroform. It is soluble in aqueous alkalis with ring cleavage, but is reconstituted upon neutralisation.

14 CLINICAL TRIALS

14.1 Efficacy and safety studies

Trial Design and Study Demographics

Table 1 – Summary of patient demographics for clinical trials in CTCL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age, years (Range)	Sex
CTCL 1	Single arm, open label	Oral methoxsalen 0.6 mg/kg body weight for up to 20 weeks; treatment on 2 consecutive days every 5 weeks and increased to treatment on 3 consecutive days every week based on response.	40	57 (24 to 80)	28 Males 12 Females
CTCL 2	Single arm, open label	Oral methoxsalen 0.6 mg/kg body weight for up to 5 years	57	63.2 (13 to 85)	34 Males 23 Females
CTCL 3	Single arm, open label	200 mcg extracorporeal UVADEX (methoxsalen) for 6 months with 6 month extension; regular treatment cycle 1 treatment on 2 consecutive days every 4 weeks; accelerated treatment 1 treatment on 2 consecutive days every 2 weeks	51	63 (33 to 77)	34 Males 17 Females

Three single-arm studies were performed to evaluate the effectiveness of photopheresis in the treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL). In the first study (CTCL 1), 39 patients were treated with the oral formulation of methoxsalen in conjunction with the UVAR Photopheresis System. The second study (CTCL 2) was a 5-year post approval follow-up of 57 CTCL patients that was conducted to evaluate long-term safety. This study also used the oral dosage formulation of methoxsalen. In the third study (CTCL 3), 51 patients were treated with the UVADEX formulation of methoxsalen in conjunction with then UVAR Photopheresis System. The total dose of methoxsalen delivered in UVADEX is substantially lower (approximately 200 times) than that used with oral administration.

In Study CTCL 1, prednisone up to 10 mg/day was permitted in addition to topical steroids. In CTCL 2, there was no concomitant medication restriction. In CTCL 3, topical steroids were permitted only for the treatment of fissures on the soles of the feet and the palms of hands. All other steroids, topical or systemic, were prohibited.

In all three studies, patients were initially treated on two consecutive days every four to five weeks. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment. Only two patients responded to treatment after six months.

Overall skin scores were used in the clinical studies of extracorporeal photopheresis (ECP) to assess the patient's response to treatment. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy.

Skin score was determined as follows:

The severity of skin lesions was determined for each of 29 body sections (similar to those used in the estimation of burn damage) from 0 to 4, according to the following scale:

0 = normal skin
0.5 = background normal, with scattered erythematous papules
1 = minimal erythema and edema; no scaling or fissuring
2 = substantial erythema and edema; no scaling or fissuring
3 = submaximal erythema, scaling, and edema; no fissuring or ectropion
4 = most severe; universal involvement with maximal erythema, edema and scaling; any fissuring or ectropion

Each severity score was multiplied by the percentage surface area to obtain a regional score. All regional scores were added together to obtain an overall lesion score.

14.2 Study results

Table 2 indicates the percent of successful responses within six months of beginning therapy for all patients who received at least one course of photopheresis. Only patients with patch plaque, extensive plaque and erythrodermic disease were enrolled in these studies. No patients with disease in the tumor phase were treated. There are no data available regarding the efficacy of UVADEX in patients with disease in the tumor phase.

Table 2 – Percentage of Successful Responses Within Six Months of Beginning Therapy

	Study CTCL 3 UVADEX ECP	**Study CTCL 2 Oral Methoxsalen + ECP**	**Study CTCL 1 Oral Methoxsalen + ECP**
Study Response (%) Within Six Months	17/51 (33)	16/57 (28)	21/39 (54)
95% CI	21 - 48	37.2 - 69.9	17 - 41.5

Although the response rate with UVADEX in Study CTCL 3 was similar to with oral methoxsalen in Study CTCL 2, the possibility that UVADEX is inferior in efficacy to oral methoxsalen cannot be excluded due to the design and size of the clinical trials. The higher response rate with oral methoxsalen in Study CTCL 1 may be partly due to patients receiving more treatments (mean of 64 in CTCL 1, 31 in CTCL 2, and 20 in CTCL 3), and to the administration of systemic steroids in Study CTCL 1.

Retrospective analyses of three clinical benefit parameters from the Body Area Severity Scores in Study CTCL 3 suggested a correlation between skin score response and improvement in edema, scaling and resolution of fissures.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The potential toxicity of combined photopheresis and UVADEX has been investigated in two preliminary studies and one definitive study in Beagle dogs.

In the first preliminary study, two Beagle dogs were treated on two consecutive days per week for two weeks with combinations of UVA light (0, 2, or 9 J/cm^2) and UVADEX 0, 200, 1000, and 2000 ng/mL buffy coat). Photoactivation time was based on individual hematocrit values and ranged from 1.2 to 2.4 hours at 2 J/cm^2 and 5.0 to 10.0 hours at 9 J/cm^2. Some decrease in body weight was observed for all dogs along with soft stool in the dogs given 2000 ng/mL of UVADEX. Effects attributable to the extracorporeal circulation of blood included decreases in erythrocyte mass, moderately to severely decreased platelet counts and increased leukocyte counts. Serum chemistry and leukocyte analysis by flow cytometric methods revealed no abnormalities which could be related to treatment. Analysis of lymphocyte viabilities suggested that treatment with 9 J/cm^2 (circulation of buffy coat through the photosette light source for at least 5 hours) resulted in a more rapid decline in the viability of cultures established from buffy coat taken immediately prior to re-infusion. There were no mortalities, no unusual clinical observations, and no gross microscopic findings which could be directly related to treatment.

In the second preliminary study, two dogs were treated daily on two consecutive days for two weeks with combinations of 1 to 2 J/cm^2 UVA and 50 ng/mL whole blood of UVADEX. The delivery rate was set to provide a blood level of >50 ng methoxsalen/mL and instrument collection volumes were adjusted to collect 150 mL blood, at the rate of 25 mL/minute, in each of two cycles. The instrument operated for about 12 minutes after each cycle volume of blood was collected. There were no changes in hematology, coagulation, or serum chemistry values which were attributable either to reinfusion leukocyte of enriched plasma or the extracorporeal circulation of blood. Analysis of lymphocyte viabilities indicated that treatment resulted in a decline in the variability of lymphocyte cultures after 7 days in culture, which was not observed in control cultures taken from two untreated dogs. Flow cytometry indicated a decrease in CD-8

lymphocytes, but the biological significance of this observation was unclear due to the small numbers of dogs studied.

In the definitive 4-week study 12 male and 12 female dogs were allocated three per sex per group to receive either placebo or UVADEX for two consecutive days a week for four weeks (total of eight treatments). One hundred and fifty (150) mL blood was collected, at the rate of 35 mL/min, from each dog in each of two cycles on each treatment occasion. UVADEX was added to provide blood levels of 100 or 500 ng/mL during UV irradiation. The photopheresis instrument delivered either 1 or 2 J/cm^2 and operated for about 12 minutes after each cycle volume of blood was collected. The total volume of blood treated each day was equivalent to about 25 to 30% of each dog's total blood volume and was similar to the proposed percentage to be collected and treated in humans. No signs of toxicity were noted in the dogs when approximately 300 mL of whole blood were removed, treated with drug, irradiated with UVA light in the photopheresis instrument and then re-infused into each donor. There were no unscheduled deaths, unusual clinical observations, or necropsy findings that could be directly related to treatment. Analysis of lymphocyte viabilities in culture resulted in the expected decline in viability after 7 days incubation thereby confirming the intended pharmacological activity of the drug treatment. There were no changes in lymphocyte subpopulations. In blood samples obtained prior to each weekly treatment and within 10 minutes after the final re-infusion of treated-blood, methoxsalen concentrations were below the minimum quantifiable concentration of 10 ng/mL.

Carcinogenicity:

Dunnick 1989 reported a carcinogenicity study in rats. The carcinogenic potential of methoxsalen was evaluated in F344/N rats treated with oral doses of 0, 37.5 and 75 mg/kg, 5 times weekly for 103 weeks. The 37.5 mg/kg dose is about 1900 times greater than a single human methoxsalen dose during extracorporeal photopheresis treatment on a body surface area basis. From Week 5 onwards the mean body weights of methoxsalen treated rats were reduced compared to controls. The survival of methoxsalen treated female rats was unaffected whereas the survival of the treated male groups was reduced compared with control males. The incidence and severity of nephropathy in treated male rats was increased and linear accumulations of foreign material were observed in the renal tubular lumina of high dose male rats. The incidence of renal tubular adenomata and adenocarcinomata was also increased in the treated male groups. There was no effect of treatment upon the incidence of either neoplastic or non-neoplastic renal lesions in treated female rats. In male rats there was also a significant positive trend for an increased incidence of subcutaneous fibromata and an increased incidence of alveolar/bronchiolar adenomata. There was also a non-dosage-dependent increase in the incidence of Zymbal's gland tumors in treated males. Parathyroid and osseous lesions typical of the secondary changes in these organs which are associated with advanced renal pathology were also observed in the treated male groups.

Genotoxicity:

Dunnick 1989 reported a series of published gentotoxicity studies performed with methoxsalen in the absence of photoactivation.

The potential of methoxsalen to induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA102, TA104 and TA1535 was tested at concentrations up to 3,333 mcg/plate both in the presence and absence of S9 mix. A mutagenic response was reported in the presence of S9 for all strains tested except TA1535. A "weak" positive response was obtained in the absence of S9 with strain TA104 whereas negative results were obtained with the other four strains.

An extended incubation protocol was used in the presence of S9 to offset cell cycle delay caused by methoxsalen in cultured Chinese Hamster Ovary (CHO) cells. Treatments in the absence of S9 at concentrations up to 250 mcg/mL produced significant increases in the frequency of chromosomal aberrations. Cell cycle time was not delayed in the presence of S9 and no increases in aberration frequency were observed at concentrations up to 600 mcg/mL. This lack of an effect may have been due to the shorter exposure time (2 hours with S9 compared to 10 hours without S9) of the cells to methoxsalen.

A significant dose-related increase in sister chromatid exchanges (SCE's) was observed over the concentration range (3.3 - 100 mcg/mL) in the absence of S9. In the presence of S9 the frequency of SCE's was increased over the range of concentrations 33 to 333 mcg/mL.

Chetélat *et al.* (1993a and 1993b) used methoxsalen as a reference standard in the development of protocols for detection of potentially photomutagenic UV absorbing compounds. Photomutagenic activity was detectable in both the Ames bacterial reversion procedure and in *Saccharomyces cerevisiae*. The extreme UV sensitivity of the excision repair-defective standard Ames tester strains however proved problematic. Exposure of CHO cells in culture to methoxsalen and UV induced cytotoxic and genotoxic effects. The magnitude of the photoclastogenic response was however dependent on the UVA dose as well as the concentration of methoxsalen.

Papadopoulo *et al*. 1983, studied cell survival, i.e. colony forming ability, and the induction of 6 thioguanine-resistant (6-TGr) mutants in Chinese hamster V79 cells. The effects of methoxsalen alone at concentrations up to 50 µM in the absence of light and the effects of 365 nm radiation (UVA) at doses up to 6 kJ/m^2 were negligible. Increases in mutant colonies were demonstrable when the cells were exposed to methoxsalen and UVA together.

Negisihi *et al*. 1992, reported that exposure of *Drosophila melanogaster* larvae to methoxsalen during irradiation with UVA enhanced the numbers of emerging flies with the mutant wing-hair spots and also showed a DNA damaging effect in the repair test using males with repair deficiency at the *mei*-9 and *mei*-41 locus and the matching repair deficient females.

The ability of PUVA to induce unscheduled DNA synthesis (UDS) in hairless mouse epidermis was investigated by Mori *et al*. 2001 in an *in vivo-in vitro* assay under carefully controlled conditions. Methoxsalen was applied to stripped epidermal skin of female hairless mice followed by UVA irradiation. Skin samples were then cultured with [^{3}H]-thymidine with or without hydroxyurea (HU) for 2 hours. In a time-course study, the UDS index was increased at 1, 2 and 24 hr after 1 x 10^{-5} J/m^2 UVA irradiation with 0.001% methoxsalen. In a dose-response study, UDS was significantly increased at the dose of 1 x 10^{-5} J/m^2 of UVA with 0.001% methoxsalen, but showed no significant change at the doses of 0.5 x 10^{-5}, 2 x 10^{-5} and 4 x 10^{-5}

J/m^2. In a further study on the effect of varying the dose of methoxsalen, the UDS index was significantly increased at 0.001 and 0.002% methoxsalen at 24 hr after 1 x 10^{-5} J/m^2 UVA irradiation, reaching the maximum level with 0.002% methoxsalen. The increase of the UDS index in these studies was less than 3 fold indicating that PUVA causes only a small induction of UDS, which might be due to slow DNA excision repair over a long period.

Gunther *et al.* 1995 investigated psoralen-induced mutagenesis in a mouse fibroblast cell line carrying a recoverable, chromosomally integrated lambda phage shuttle vector. Using the *sup*F gene as a mutation reporter gene, the spectrum of mutations induced by photoactivation of methoxsalen (5 µM) was determined. Predominately T:A to A:T and some T:A to G:C transversions were generated. Most of the mutations occurred at either 5' TpA or 5' ApT sites, both of which are conducive to interstrand cross-link formation. Methoxsalen generated 20% cross-links and 80% monoadducts as measured by direct HPLC analysis of the DNA from the treated cells. Although most of the mutations occurred at potentially cross-linkable sites, these results implicate monoadducts, as well as cross-links, as critical premutagenic lesions in psoralen-treated mammalian cells.

Reproductive and Developmental Toxicology:

In an embryo-fetal development study methoxsalen was administered orally to rats at doses of 0, 20, 80, 120, and 160 mg/kg/day on Days 6-15 of pregnancy. Rats were sacrificed on Day 20, fetuses removed and examined for evidence of developmental toxicity. There was no maternal mortality during the study. Maternal relative food consumption was markedly suppressed (44-64%) during methoxsalen treatment at doses from 80 mg/kg/day but returned to and exceeded (55%) control values from Day 18. Maternal relative water consumption groups was significantly reduced (23%) on Days 6 to 9 in the 120 and 160 mg/kg/day groups returning to or exceeding control values by Day 12 to 15. Water intake was elevated in the three highest dose groups from Days 18 to 20. Methoxsalen at doses from 80 mg/kg/day produced a significant and dose related reduction in maternal body weight from Day 9 through to sacrifice on Day 20. Relative maternal liver weight was significantly increased at doses from 80 mg/kg/day and above. No maternal measure was significantly altered by 20 mg/kg/day methoxsalen.

Methoxsalen caused significant fetotoxicity. At the 160 mg/kg/day dose resorptions per litter were increased and live litter size and average fetal weight were both significantly reduced. A significant trend toward an increase in the incidence of fetuses with malformations per litter and litters with malformations was noted. Enlarged lateral ventricles of the brain were the major contributor to this increase. However, the overall incidence of malformations was not significantly increased relative to concurrent controls, and was within the historical control range, except at 160 mg/kg/day. The percent of fetuses per litter with variations was significantly increased in the 120 mg/kg/day (217%) and 160 mg/kg/day (320%) groups. The incidence of rudimentary lumbar 1 rib was the only variation which showed a dose-dependent increase. Methoxsalen at 20 and 80 mg/kg/day did not adversely affect fetal development.

The Lowest Observable Adverse Effect Level (LOAEL) for methoxsalen-induced maternal toxicity was 80 mg/kg/day and the No Observable Adverse Effect Level (NOAEL) was 20 mg/kg/day.

A series of studies has investigated the reproductive toxicity of the psoralens in Wistar rats. Initial experiments indicated that methoxsalen at dietary concentrations of 250 ppm significantly reduced growth rate in males and females and at 1250 ppm, birth rates were significantly reduced.

To further investigate the cause of reduced birthrate, methoxsalen 1250 or 2500 ppm was administered in the diet to female rats (mated to undosed males) from Day 21 of age to parturition. The numbers of implantation sites, pups, corpora lutea and uterine weight were significantly reduced in dosed females compared with control animals and there was a significant dose-related reduction in circulating estrogen levels. In addition mRNAs of liver enzymes were induced suggesting that enhanced oxidative metabolism and conjugation of estrogens in psoralen-treated animals may provide a partial explanation for the reproductive toxicity, reduction in ovarian follicular function and ovulation. Histological examination of ovaries in non-pregnant female rats treated with methoxsalen 180 mg/kg/day orally for 30 days indicated that methoxsalen targets the follicle and its granulosa cells at the antral stage thereby reduces 17-beta estradiol production.

The potential for apoptosis as the mechanism of methoxsalen-mediated ovarian toxicity was examined in female rats treated with control or 180 mg/kg/day orally for twelve weeks. A significant decrease in protein levels of both aromatase (marker of follicular apoptosis) and caspase-3 (executioner of ovarian atresia) was observed in methoxsalen treated rats compared with the control. Histological analysis also confirmed follicular damage typical of apoptotic-stimulating agents in antral follicles. These findings are consistent with increased levels of oxidative DNA damage and moreover, disruption of the hypothalamic-pituitary-gonadal axis.

The effects of methoxsalen on reproductive function in male Wistar rats (10/group) was assessed following oral administration of methoxsalen (in diet) at doses of 0, 75 and 150 mg/kg/day for eight weeks. Methoxsalen treated males had significantly smaller pituitary glands and fewer sperm per ejaculate in the vasa deferentia and epididymides than controls. Testosterone levels and relative testis weights were significantly increased. Females bred with methoxsalen treated males required more time to become pregnant and males required more breeding attempts.

Following on from the above study, a modified comet assay protocol was used to test rat spermatozoal DNA for methoxsalen-induced damage. Spermatozoa samples from mature Wistar rats were reacted with methoxsalen 0, 2, 4, 6, 8, 10 mg/mL acetone solution with and without exposure to long-range UVA radiation. Methoxsalen treated, irradiated and non-irradiated sperm samples sustained significantly more damage than untreated, irradiated samples and the damage was dose-dependent.

Special Toxicology:

Inhibition of scheduled DNA synthesis appears to be central to the intended pharmacological effects of methoxsalen when used in combination with UVA for the treatment of CTCL.

Results from DNA binding studies have demonstrated that approximately 68% of added methoxsalen covalently binds to DNA. This represents a greater than 25-fold increase in the

binding of photoactivated methoxsalen compared with the DNA binding found in the absence of photoactivation.

Maeda et al. 2005 investigated whether extracorpeal photopheresis exhibits the capacity to induce Ag-specific regulatory T cells (Tr). For this purpose an in vivo model of photopheresis using a murine model of contact hypersensitivity was established, whereby splenocytes and lymph node cells of C3H/HeN mice and BALB/c female mice were sensitized with dinitrofluorobenzene (DNFB), exposed to methoxsalen/UVA, injected into recipients and the ear swelling response measured.

Transfer of cells from primary recipients that had received cells exposed to methoxsalen/UVA significantly suppressed the DNFB response in the secondary recipients. In contrast, transfer of cells from primary recipients that had received cells exposed to nothing, UVA alone or methoxsalen alone did not suppress the DNFB response in the secondary recipients. The fact that the suppression can be adoptively transferred from primary into secondary recipients suggests that the infusion of methoxsalen/UVA treated cells induce cells with regulatory activity in the primary recipients.

To determine whether these transferred cells cause suppression in a hapten-specific fashion, the experiment described was repeated, however the mice were OXA (oxazolone) sensitized rather than sensitized with DNFB. Although these animals retained the ability to suppress DNFB mediated ear swelling, they were incapable of decreasing the OXA-mediated ear swelling. This indicates that the infusion of methoxsalen/UVA-treated splenocytes obtained from DNFB-sensitized donors induces Ag-specific regulatory cells in the primary recipients.

Mays et al. 1987, compared the i.v. pharmacokinetics of [14C]-methoxsalen 10 mg/kg in male Sprague Dawley rats (n=3/group) which were either naive (controls) or pre-treated for three days with methoxsalen 70 mg/kg i.p. Control rats showed a typical curvilinear decline in plasma radioactivity whereas the methoxsalen pre-treated group eliminated an i.v. dose more rapidly suggesting that methoxsalen had the ability to induce its own metabolism in vivo.

In an early study by Kolis et al. 1979 in three male beagle dogs given single i.v. doses of 5 mg/kg [14C] methoxsalen, the compound was eliminated from plasma with a half-life of 3.4 hours. Radioactivity was measurable in plasma for up to 35 days and the plasma half-life for total radioactivity was estimated to be 6.8 days.

In later studies by Monbaliu et al. 1988 in 6 mongrel dogs using unlabelled compound and a sensitive HPLC UV method (detection limit about 10 ng/mL), pharmacokinetic parameters were derived following i.v. administration of 2 mg/kg methoxsalen. In most dogs the plasma concentration-time profile declined biexponentially but the derived pharmacokinetic parameters varied considerably between the different dogs. The mean half-lives of distribution and elimination were 0.20 hours and 2.17 hours respectively. The average total plasma clearance was 0.51 L/kg/hour. Estimates of dose-normalized AUC values obtained after i.v. bolus injections of 1, 3, and 10 mg/kg demonstrated that the plasma kinetics of intravenously administered methoxsalen were non-linear in the dog.

Results of autoradiographic studies show that in rats psoralens distribute into most organs but binding appears to be short-lived and reversible. Other studies in the rat have shown the

highest concentrations of active substance in the liver and kidneys and a fat/muscle ratio of 3:1. Binding to human albumin is high (80-90%).

The time course of the uptake and elimination of methoxsalen in the epidermis and lens of guinea pigs following 15 mg/kg orally has been investigated by Wamer et al. 1987. Orally administered methoxsalen diffuses rapidly into and out of the epidermis and there is a good correlation between serum and epidermal methoxsalen concentrations. The uptake and elimination of methoxsalen by the lens lagged significantly behind that in serum and the epidermis. The concentration of methoxsalen in the lens peaked (790 ng/g) at 3 hours and concentrations were maintained for at least three hours thereafter. The concentration of methoxsalen in serum was unquantifiable at 18 hours whereas methoxsalen remained quantifiable in both the epidermis (66 ng/g) and lens (78 ng/g) at this time point.

Malinin et al. 1982, investigated the tissue distribution of [14C]-methoxsalen in female rabbits after a single intravenous dose of 5 mg/kg followed by irradiation of skin. Peak radioactivity was found at 1 hour in the kidney, at 2 hours in the liver, but only at 8 hours in the bile. Radioactivity was generally low in the pancreas, adrenals, thyroid, pituitary, skeletal and cardiac muscle, brain, and lymphatic tissues. In the gastro-intestinal tract the highest amounts of radioactivity were measurable in the small intestine and esophagus. The highest amount of radioactivity was measured in irradiated skin at 1 hour with a progressive decline thereafter to 280 ng equiv/g at 24 hours. In non-irradiated skin there was less radioactivity present and the 1 hour peak was absent. Autoradiography of liver and kidney at 1 hour after dosing indicated predominantly interstitial and intracytoplasmic localisation of radioactivity.

The potential for methoxsalen to induce metabolism was examined by Mays et al. 1987 in liver from naive (control) rats and from rats pretreated for 3 days with methoxsalen 70 mg/kg/day i.p. Metabolism of methoxsalen was demonstrated in the 9000 g supernatant from liver homogenate and in liver microsomes, and was shown to be inducible by pretreatment with methoxsalen. During the first 10 minutes of incubation with 9000 g supernatant, methoxsalen disappeared at the rate of 24 pmol/min/mg of protein, and acetone-extractable metabolites appeared at the rate of 15 pmol/min/mg of protein. Corresponding control values were 7 and 5 pmol/min/mg of protein respectively. Similarly during the first 2 minutes of incubation with liver microsomes methoxsalen disappeared at the rate of 0.38 nmol/min/mg of protein and metabolites appeared at the rate of 0.18 nmol/min/mg of protein compared with control rates of 0.22 for methoxsalen and 0.16 for metabolites respectively. It was suggested that the observed pattern of results, especially the rapidity with which the reaction slows down, may be consistent with inactivation of cytochrome P450 by the formation of one or more reactive metabolites.

Bickers et al. 1982 investigated the effects of methoxsalen on hepatic drug metabolizing enzymes and cytochrome P450 in mice and rats. Methoxsalen 0.8 mg/kg/day administered orally to CD 1 mice for 6 days caused 2-3 fold increases in hepatic aryl hydrocarbon hydroxylase (AHH), ethylmorphine N demethylase and cytochrome P450. The absorbance maximum of the induced cytochrome was at 450 nm. Aniline hydroxylase activity was unchanged. In Sprague Dawley rats after the same dosage regimen methoxsalen caused a greater than 4-fold enhancement of AHH and greater than 2-fold enhancement of ethylmorphine N-demethylase

and cytochrome P450. Chronic administration of methoxsalen 1.2 mg/kg/day for 6 weeks to hairless mice caused significant enhancement of hepatic ethylmorphine N-demethylase and cytochrome P450 but had no effect on AHH. Comparisons were made in mice of the effects of methoxsalen (0.8 mg/kg/day x 6 p.o) with those of phenobarbital (75 mg/kg/day x 3 p.o.) a known cytochrome P450 inducer and 3 methylcholanthrene (40 mg/kg/day x 3 p.o.) a known cytochrome P448 inducer. The behaviour of methoxsalen was similar to but less pronounced than that of phenobarbital.

Mandula et al. 1978 investigated the ability of methoxsalen to induce mixed function oxidases in the liver of male CD-1 mice in comparison to phenobarbital. Methoxsalen 100 mg/kg orally or i.p. induced a 2.5 to 3-fold increase in p-nitroanisole-O-demethylase activity and a small increase in AHH activity. Responses of similar magnitude were reported following administration of the same dose (100 mg/kg) of phenobarbital indicating that methoxsalen is an inducer of p nitroanisole-O-demethylase but not of AHH.

In a study in male Sprague Dawley rats treated i.v. with 10 mg/kg [14C] methoxsalen Mays et al. 1987, detected 13 peaks, by HPLC, in the urine. Five of these peaks were identified as methoxsalen, 5 HMP (5 hydroxy-8-methoxypsoralen), 8 HOP (8 hydroxypsoralen), DHP (5,8 dihydroxypsoralen)/DOP (5,8 dioxypsoralen) and HCA (6 (7 hydroxy-8-methoxycoumaryl)-acetic acid). Two further peaks were identified as a sulphate conjugate of 5-HMP and a demethylated sulphate conjugate of DHP.

Kolis et al. 1979 investigated the metabolism of [14C]-methoxsalen in male beagle dogs following a single i.v. dose of 5 mg/kg. At 24 hours after dosing less than 2% of plasma radioactivity represented unchanged methoxsalen. Four urinary metabolites of methoxsalen were isolated, and identified. Three of the urinary metabolites resulted from the opening of the furan ring: these were 7 hydroxy-8-methoxy-2-oxo-2N-1-benzopyran-6-acetic acid (A), □,7-dihydroxy-8-methoxy-2-oxo-2N-1-benzopyran-acetic acid (B), and an unknown conjugate (C) of A at the 7-hydroxy position. The fourth metabolite (C), formed by opening of the pyrone ring, was an unknown conjugate of (Z) 3-(6-hydroxy-7-methoxybenzofuran-5-yl)-2-propenoic acid. In the bile approximately one-third of the radioactivity consisted of the metabolites found in urine with the major components being metabolites C and D. Less than 1% of the biliary radioactivity was unchanged methoxsalen. These results indicated that in the dog, the important routes of metabolism are furan and pyrone ring scission followed by conjugation.

In the rat following oral administration of [3H]-methoxsalen 6 mg/kg, radioactivity was excreted primarily in urine with 55% of the dose recovered in 12 hours and 66% in 96 hours. Fecal excretion accounted for 15.3% of the radioactivity in 96 hours. In bile duct-cannulated rats, 100% of the radioactivity given as an oral dose of [3H]-methoxsalen was recovered in the urine indicating biliary excretion in the region of 35% of the dose.

Malinin et al. 1982 quantified the excretion of radioactivity in the urine of female rabbits after a single intravenous dose of 5 mg/kg [14C]-methoxsalen. The peak concentration of radioactivity occurred at 1 hour after dosing, declining progressively thereafter, but still persisting in 24 hour samples.

In the dog 44.8% and 39.9% of the administered radioactivity was recoverable in the urine and feces respectively during the first three days after an i.v. dose 5 mg/kg of [14C]-methoxsalen. Biliary excretion accounted for 19% of the administered radioactivity during the first 5 hours after dosing. The extent of biliary excretion in the dog is apparently greater than found in man.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrUVADEX®

Methoxsalen Sterile Solution

Read this carefully before you start taking UVADEX and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about UVADEX.

Serious Warnings and Precautions

Possible serious side effects with UVADEX include:

- Skin cancer.
- Damage to the genetic material in cells (DNA).
- Harm to an unborn baby.
- Cataract (a clouding of the lens inside the eye which leads to reduced vision).
- Skin burning.

What is UVADEX used for?

UVADEX is used to treat adults with skin symptoms of Cutaneous T-cell lymphoma (CTCL) when other treatments are not effective. CTCL is a blood disorder causing abnormal growths affecting the skin.

How does UVADEX work?

UVADEX is used with the THERAKOS CELLEX Photopheresis System.

A small amount of your blood is collected during treatment. The white blood cells from the collected blood are mixed with a calculated dose of UVADEX. This mixture is exposed to UV light in the THERAKOS CELLEX Photopheresis System, then your blood is returned to you. The UV light activates UVADEX. This process may help your CTCL skin symptoms.

What are the ingredients in UVADEX?

Medicinal ingredients: methoxsalen

Non-medicinal ingredients: Alcohol 95%, glacial acetic acid, propylene glycol, sodium acetate trihydrate, sodium chloride, sodium hydroxide, and water for injection

UVADEX comes in the following dosage forms:

Sterile Solution, 20 mcg/mL

Do not use UVADEX if:

- You are allergic to methoxsalen or any other ingredient in UVADEX.
- You are allergic to psoralen compounds.
- You have a history of a light sensitive disease state, such as:
  - Lupus erythematosus, a severe form of skin inflammation.
  - Porphyria cutanea tarda, a disorder that causes the skin to be very sensitive to light.
  - Erythropoietic protoporphyria, a disorder that causes a burning and itching sensation on the surface of the skin.
  - Variegate porphyria, a disorder that causes vomiting, diarrhea, constipation, and skin damage.
  - Xeroderma pigmentosum, a very rare skin disorder that causes a high sensitivity to sunlight, premature skin aging and the development of skin cancers.
  - Albinism, a disorder that causes a lack of pigmentation in the hair, skin and eyes.
- You have aphakia. This is a condition where you are missing the lens in your eye(s).
- You have severe heart problems.
- You have anemia (a low red blood cell count).
- You have a high white blood cell count (greater than 25,000 mm^3).
- You have had your spleen surgically removed. The spleen is an organ that helps filter your blood.
- You have coagulation disorders (your blood has trouble forming clots).
- You have an existing skin cancer.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take UVADEX. Talk about any health conditions or problems you may have, including if you:

- Are taking medicines that make you sensitive to the sun.
- Have cataracts.
- Have liver problems.
- Are pregnant or think you might be pregnant. It is not known if UVADEX will harm your unborn baby.
- Are breast-feeding. It is not known if UVADEX passes into breast milk.

Other warnings you should know about:

Before starting treatment with UVADEX, your healthcare professional will check your health status. They will review your medical conditions, medicines you are taking and platelet count.

During treatment with UVADEX, the needle may stop working. Your healthcare professional is trained to recognize and manage this possible side effect should it occur.

Skin problems

After treatment with UVADEX, exposure to sunlight and/or ultraviolet radiation may cause skin damage. For example, skin burning, premature skin aging, or skin cancer (in the long term).

For 24 hours after each treatment, you are recommended to avoid sun exposure by:

- Wearing UVA absorbing, wrap-around sunglasses; and
- Covering exposed skin or using a sun-block (SPF 15 or higher).

Follow these steps any time you are exposed to direct or indirect sunlight, indoors and outdoors.

Birth control

Men and women should use an effective method of birth control both during and after completion of UVADEX treatment.

Fertility

It is not known if UVADEX has an effect on fertility. Talk to your doctor if this is a concern for you.

Driving and using machines

Do NOT drive or use machines immediately after treatment with UVADEX.

Treatment with UVADEX is likely to affect your ability to drive or use machines. Before you do tasks that require special attention, wait until you know how UVADEX affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with UVADEX:

- Fluoroquinolones, nalidixic acid, sulfonamides tetracyclines – medicines used to treat bacterial infections
- Antipyrine, paracetamol – medicines used to treat pain
- Tolbutamide and other sulfonylureas – medicines used to control blood sugar
- Phenytoin – medicine used to treat seizures
- Dicoumarol, warfarin – medicines used to thin the blood
- Promethazine – medicine used to treat allergies
- Furosemide, thiazides – medicines used to treat fluid retention, increased blood pressure and cardiac disorders
- Phenothiazine – medicine to treat agitation
- Anthralin, coal tar or coal tar derivatives, retinoids – medicines used to treat skin conditions
- Halogenated salicylanilides – soaps that inhibit the growth of bacteria

- Griseofulvin – medicine used to treat skin infections
- Methylene blue, methyl orange, toluidine blue, rose Bengal – organic staining dyes used to identify certain body tissues
- Caffeine – used to increase alertness and wakefulness

How to take UVADEX:

UVADEX will be given to you by a healthcare professional using the THERAKOS CELLEX Photopheresis System, in a healthcare setting.

Usual dose:

- Your healthcare professional will calculate the amount of UVADEX that your cells will be treated with during the procedure.
- The usual treatment schedule is 2 consecutive days once a month for six months.
- After around 3 months of treatment, your healthcare professional will assess your response to the treatment. If they decide you need to be treated more frequently, your schedule may be adjusted to 2 treatments every 2 weeks.
- You may receive a total of 40 treatments.

Overdose:

In the event of overdosage, you should remain in a darkened room for at least 24 hours.

If you think you, or a person you are caring for, have been given too much UVADEX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using UVADEX?

These are not all the possible side effects you may have when taking UVADEX. If you have any side effects not listed here, tell your healthcare professional.

Side effects of UVADEX and/or the treatment procedure (photopheresis) may include:

- Dizziness
- Nausea
- Vomiting
- Pain or swelling at the site of injection
- Sensitivity to sunlight
- Altered taste

Contact your doctor if you begin to show signs of infection such as fever, chills, or pain or swelling at the site of injection.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue [may occur when you go from lying or sitting to standing up]		X	
UNKNOWN			
Anemia (low red blood cell levels): shortness of breath, fatigue, having pale skin, irregular heartbeats, loss of energy, or weakness.		X	
Allergic reaction: itchiness, redness of skin, swelling, flushing, labored breathing, heart racing, chest pain, high blood pressure		X	
Skin cancer: unusual, skin growths that do not go away or heal; changes in size, shape, or color of an existing spot on the skin.			X
Cataract (a clouding of the lens inside the eye which leads to reduced vision)**:** clouded, blurred, or dim vision			X
Skin burning: red skin, skin blisters, or skin peeling after exposure to sunlight or UV light	X		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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.

Storage:

UVADEX will be managed and stored by healthcare professionals. The information on how to store UVADEX is meant for your healthcare professional.

Store between 15 to 30°C.

Keep out of reach and sight of children.

If you want more information about UVADEX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website mallinckrodt.ca/products/therakos, or by calling 1-877-566-9466.

This leaflet was prepared by Therakos, Inc.

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