

Surrounded by Support

Dedicated access to people who can help



INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CAUTION: READ THE THERAKOS UVAR XTS or THERAKOS CELLEX PHOTOPHERESIS SYSTEMS' OPERATOR'S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION.

UVADEX (methoxsalen) Sterile Solution should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience in the THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis System. Please consult the appropriate Operator's Manual before using this product.

Please see Important Safety Information and accompanying Full Prescribing Information, including the BOXED WARNING for UVADEX, and see the appropriate THERAKOS Photopheresis System Operator's Manual.



IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

UVADEX is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, other psoralen compounds, or any of the excipients. 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.

Patients should not receive UVADEX if they have any contraindications to the photopheresis procedure.

WARNINGS AND PRECAUTIONS

- 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 may be at greater risk for photosensitivity reactions with UVADEX
- Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair
- Methoxsalen may cause fetal harm when given to a pregnant woman. 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. It is not known whether this drug is excreted in human milk
- After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin
- Since oral psoralens may increase the risk of skin cancers, monitor closely those patients who exhibit multiple basal cell carcinomas or who have a history of basal cell carcinomas
- Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions are not followed
- Patients should be advised to avoid all exposure to sunlight during the 24 hours following photopheresis treatment
- Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity. 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
- Instruct patients emphatically to wear UVA-absorbing, wrap-around sunglasses for 24 hours after UVADEX treatment
- Safety in children has not been established
- Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, have been reported with UVADEX administration through photopheresis systems for treatment of patients with graft-versus-host disease, a disease for which UVADEX is not approved.

ADVERSE REACTIONS

- Side effects of photopheresis (UVADEX used with the THERAKOS Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%)

For the THERAKOS® UVAR XTS®/CELLEX® Photopheresis Procedure:

INDICATIONS

The THERAKOS UVAR XTS Photopheresis System/THERAKOS CELLEX Photopheresis System is indicated for use in the ultraviolet-A (UVA) irradiation, in the presence of the photoactive drug 8-methoxypsoralen (8-MOP®), of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL), in persons who have not been responsive to other forms of treatment.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

The THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis Systems are not designated, sold, or intended for use except as indicated.

Certain underlying medical conditions contraindicate THERAKOS Photopheresis, including patients:

- who cannot tolerate extracorporeal volume loss during the leukocyte-enrichment phase
- exhibiting idiosyncratic or hypersensitivity reactions to 8-methoxypsoralen/psoralen compounds
- with coagulation disorders
- who have had previous splenectomy

WARNINGS AND PRECAUTIONS

- THERAKOS Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure
- Patients who may not be able to tolerate the fluid changes associated with extracorporeal photopheresis should be monitored carefully
- Procedures, such as renal dialysis, which might cause significant fluid changes (and expose the patient to additional anticoagulation) should not be performed on the same day as extracorporeal photopheresis
- Individual patients may require a heparin dosage that varies from the recommended dose to prevent post-treatment bleeding or clotting during a treatment

ADVERSE REACTIONS

- Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for hypotension
- Transient pyretic reactions, 37.7-38.9°C (100-102°F), have been observed in some patients within six to eight hours of reinfusion of the photoactivated leukocyte-enriched blood. A temporary increase in erythroderma may accompany the pyretic reaction
- Treatment frequency exceeding labeling recommendations may result in anemia
- Venous access carries a small risk of infection and pain

Please see accompanying Full Prescribing Information including the BOXED WARNING for UVADEX, and see the appropriate THERAKOS Photopheresis System Operator's Manual.

THERAKOS® Total Care Can Help You Stay Focused on Patient Care



ECP customer care is here to help 24/7/365

1-877-566-9466

Please see Important Safety Information on pages 1-3, accompanying Full Prescribing Information, including the BOXED WARNING for UVADEX, and appropriate THERAKOS Photopheresis System Operator's Manual.

ACCESS TO SERVICES THAT HELP SUPPORT YOUR USE OF THE THERAKOS PHOTOPHERESIS SYSTEM

We understand that providing extracorporeal photopheresis (ECP) therapy for the palliative treatment of CTCL skin manifestations can be a complex undertaking.

For this reason, we feel it is important for us to make support services available to our customers. As a CELLEX and Photopheresis System customer, you have complementary access to the following services, with the exception of post-warranty on-site technical services, which are available for an incremental charge.



	CUSTOMER CARE	A 24/7/365 primary point of contact to place orders and respond to customer inquiries
	PRODUCT SUPPORT	Live professional phone support and access to product information
	TECHNICAL SERVICES*	Expert instrument installation and service
	CLINICAL SPECIALISTS	Professional clinical educators to provide your instrument operators with THERAKOS Photopheresis-specific training and education
	CONTRACT SUPPORT	Dedicated team to help manage the contracting process
	EDUCATIONAL RESOURCES	Access to patient education tools and medical professional education programs

* Additional charges will apply for post-warranty on-site service. Contact a Customer Care representative for more information.



Support Services With a Personal Touch



Service information available through one phone number all day long

1-877-566-9466

Please see Important Safety Information on pages 1-3, accompanying Full Prescribing Information, including the BOXED WARNING for UVADEX, and appropriate THERAKOS Photopheresis System Operator's Manual.

CUSTOMER CARE: YOUR CONSISTENT POINT OF CONTACT



People familiar with your account available to help 24/7/365

- Quick answers about your account and access to further assistance
- Certificate of Analysis requests are processed the same day
- Order support for the CELLEX® instrument, procedure kits, UVADEX® (methoxsalen) Sterile Solution, and other materials

PRODUCT SUPPORT: FOR ECP SYSTEM-RELATED QUESTIONS



Trained professionals available to help

- Knowledgeable professionals are just a phone call away to address product-related questions
- Focused on supporting best practices and helping you find answers to your product questions

TECHNICAL SERVICES: FOR INSTRUMENT INSTALLATION AND SERVICE*



Responsive field engineers are ready to help

- New instrument installation support
- Rapid responses to service requests help deliver a best-in-class experience
- Installation of software upgrades as available
- Regular preventive maintenance services are available

* Additional charges will apply for post-warranty on-site service. Contact a Customer Care representative for more information.

CLINICAL SPECIALISTS: FOR OPERATOR TRAINING



Personalized attention from clinical specialists with on-site instruction

- Two training sessions per year tailored to your operator educational needs
- On-site professional training helps get new staff up to speed
- Self-assessment tools are also available

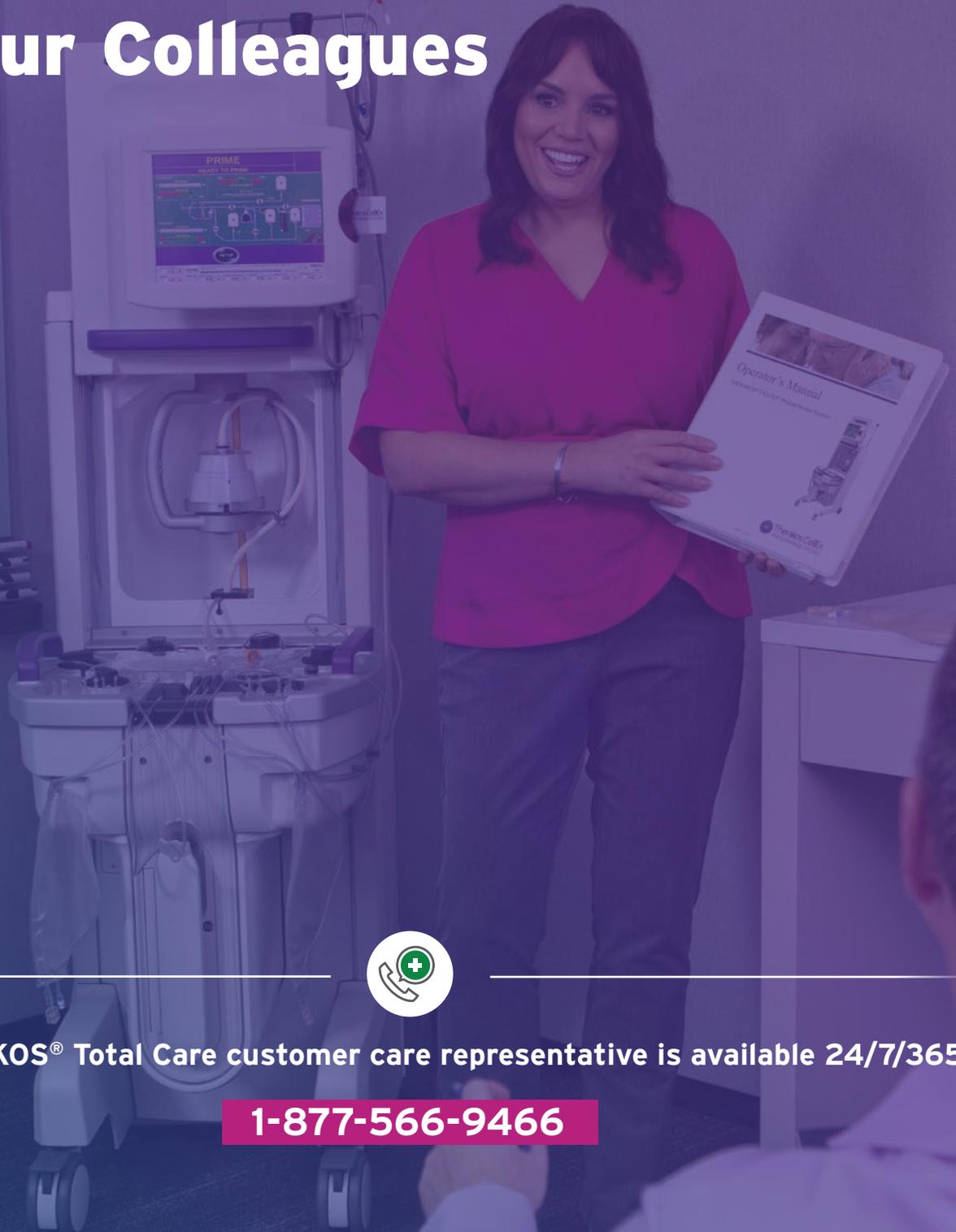
CONTRACT SUPPORT: FOR PROCUREMENT AND COST-CENTER NEEDS



Experienced contract managers help you handle the details

- Provide contract options and pricing for both product and service needs
- Learn about special programs (eg, multi-instrument discounts) that may be available at the time of instrument purchase
- Documentation support helps you track service history
- Help you to decide if product and/or service agreements are right for you

Educational Resources to Support You and Your Colleagues



A THERAKOS® Total Care customer care representative is available 24/7/365

1-877-566-9466

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HELPING YOU STAY INFORMED



Speaker Events

Local experts are available for a peer education session covering:

- 1: Concepts in understanding and identifying the skin manifestations of CTCL
- 2: ECP for the treatment of skin manifestations of CTCL

Speak to a company representative about how to host or attend a speaker program.



Vascular Access Reference Guide

Information about vascular access devices that may align with THERAKOS Photopheresis System requirements for your consideration.



MyTHERAKOS.com Portal

Customer-only portal for access to operator manuals, technical bulletin updates, and operator training resources.

HELPING TO INCREASE AWARENESS OF ECP



Treatment Center Outreach Resources

Resources to support service awareness initiatives. Additional team support for open house/awareness events may be available upon request.



Extracorporeal Photopheresis Treatment Center Directory

Regularly updated directory that is also available online with a list of facilities offering THERAKOS Photopheresis.*

*Treatment centers are independent, third-party facilities not owned, operated, or controlled by Mallinckrodt Pharmaceuticals. This resource is provided for informational use only and may not be comprehensive.

Resources to Support Your Patient Education Efforts



Get downloadable resources for your patients at

www.therakos.com

For purposes of illustration.

Please see Important Safety Information on pages 1-3, accompanying Full Prescribing Information, including the BOXED WARNING for UVADEX, and appropriate THERAKOS Photopheresis System Operator's Manual.

HELPING PATIENTS START TREATMENT



Patient Starter Kit

For patients initiating treatment, the patient starter kit includes the Action Plan brochure along with treatment support items, such as a squeeze ball, a fleece blanket, a sunscreen sample, and sunglasses.



Treatment Access Support Brochure

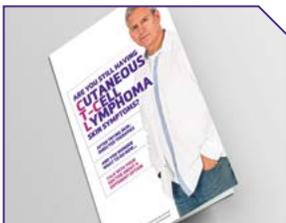
This brochure provides information regarding a Mallinckrodt patient assistance program administered through the National Organization for Rare Disorders (NORD). To learn more about the program and determine if your patient may qualify, email photopheresis@rarediseases.org or call 1-877-241-7220.

HELPING PATIENTS UNDERSTAND TREATMENT



Nurse Counseling Tools

A series of counseling cards that healthcare professionals may choose to share with patients to help them understand CTCL skin symptoms, how to prepare for treatment, and the importance of adhering to their prescribed care plan.



Decision Aid Brochure

This brochure may help your patients understand what they may expect during treatment and help them prepare questions regarding photopheresis treatment.



Action Plan Brochure

This brochure was designed to help patients prepare for treatments, keep track of appointments, and communicate with their healthcare professional.



Patient Website

The website patient.therakos.com has patient-friendly information about CTCL skin symptoms and digital resources to help support patients through their treatment, as well as videos of people living with CTCL skin symptoms who have found relief through photopheresis.



Therakos[®]
PHOTOPHERESIS

Total
care

Surrounding You With Support

Committed to helping you focus on patient-centric care



With you
from installation
through training and
instrument care



Training and resources
for all customers to
help support positive
experiences



Continuous support
with contract- and
instrument-related
questions helps relieve
the logistical burden



**A THERAKOS customer care
representative is available 24/7/365**

1-877-566-9466

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www.therakos.com
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UVADEX®

(Methoxsalen)

STERILE SOLUTION, 20 mcg/mL

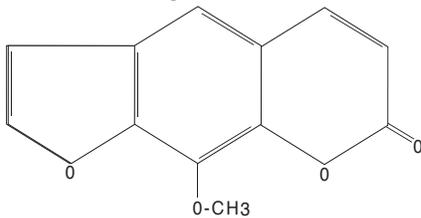
Rx ONLY.

CAUTION: READ THE THERAKOS® UVAR XTS® or THERAKOS® CELLEX® PHOTOPHERESIS SYSTEM OPERATOR'S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION.

UVADEX® (methoxsalen) Sterile Solution should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience in the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System. Please consult the appropriate Operator's Manual before using this product.

DESCRIPTION

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the Ammi majus (Umbelliferae) plant. It belongs to a group of compounds known as psoralens or furocoumarins. The chemical name of methoxsalen is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one; it has the following structure:



Each mL of UVADEX® (methoxsalen, 8-methoxypsoralen) Sterile Solution contains methoxsalen 20 mcg, propylene glycol 50 mg, sodium chloride 8 mg, sodium acetate 1.75 mg, ethanol 40.550 mg, glacial acetic acid 1.260 mg, and Water for Injection q.s. to 1.0 mL. Glacial acetic acid and sodium hydroxide are used to adjust the pH of the solution if necessary. UVADEX® is a clear, colorless to pale yellow liquid.

UVADEX® is used in combination with the THERAKOS® UVAR XTS® and THERAKOS® CELLEX® Photopheresis Systems to extracorporeally treat leukocyte enriched buffy coat.

CLINICAL PHARMACOLOGY

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. The formation of photoadducts results in inhibition of DNA synthesis, cell division and epidermal turnover.

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 the UVADEX® Sterile Solution 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. See the appropriate Operator's Manual for details of this process. Although extracorporeal phototherapy exposes less than 10% of the total body burden of malignant cells to methoxsalen plus light, some patients achieve a complete response. Animal studies suggest that the photopheresis may activate an immune-mediated response against the malignant T-cells.

Use of the UVAR and UVAR XTS® Systems after oral administration of methoxsalen were previously approved for the treatment of Cutaneous T-Cell Lymphoma. 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.

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.

Systemic administration of methoxsalen followed by UVA exposure leads to cell injury. The most obvious manifestation of this injury after skin exposure is delayed erythema, which may not begin for several hours and peaks at 48–72 hours. The inflammation is followed over several days to weeks, by repair which is manifested by increased melanization of the epidermis and thickening of the stratum corneum.

The total dose of methoxsalen delivered in UVADEX® is substantially lower (approximately 200 times) than that used with oral administration. More than 80% of blood samples collected 30 minutes after reinfusion of the photoactivated buffy coat had methoxsalen levels below detection limits of the assay (<10 ng/ml), and the mean plasma methoxsalen concentration was approximately 25 ng/ml.

CLINICAL STUDIES

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 the UVAR Photopheresis System. In study CTCL 3, 86% of the patients were Caucasian, the median age was 62 years, and the average number of prior therapies was 4.3.

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. If the patient did not respond after four cycles, treatment was accelerated to two consecutive days every other week. If the patient did not respond after four cycles at the accelerated schedule, the patient was treated on two consecutive days every week. If the patient still did not respond after four cycles of weekly treatments, the schedule was increased to three consecutive days every week for three cycles. 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. Clinical experience does not extend beyond this treatment frequency and there is no evidence to show that treatment with UVADEX® beyond six months or using a different schedule provided additional benefit.

Overall skin scores were used in the clinical studies of photopheresis to assess the patient's response to treatment. The patient's baseline skin score was used for comparison with subsequent scores. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy. Table 1 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 1:
Percentage of Successful Responses
Within Six Months of Beginning Therapy**

Study	Response % Within Six Months
CTCL 3 (UVADEX®)	17/51 (33)
CTCL 2 (oral methoxsalen)	16/57 (28)
CTCL 1 (oral methoxsalen)	21/39 (54)

Although the response rate with UVADEX® in CTCL 3 was similar to with oral methoxsalen in 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 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 CTCL 1.

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

INDICATIONS AND USAGE

UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the THERAKOS® UVAR XTS® or 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.

CONTRAINDICATIONS

PHOTOSENSITIVITY: UVADEX® (methoxsalen) Sterile Solution is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, other psoralen compounds or any of the excipients. 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® Sterile Solution is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses.

Patients should not receive UVADEX® if they have any contraindications to the photopheresis procedure.

WARNINGS

Concomitant Therapy: 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 may be at greater risk for photosensitivity reactions with UVADEX®.

Carcinogenicity, Mutagenesis, Impairment of Fertility: 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.

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.

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.

Pregnancy: 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/m² 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.

PRECAUTIONS

General: ACTINIC DEGENERATION:

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

BASAL CELL CARCINOMAS:

Since oral psoralens may increase the risk of skin cancers, monitor closely those patients who exhibit multiple basal cell carcinomas or who have a history of basal cell carcinomas.

SERIOUS SKIN BURNS:

Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions are not followed. Advise patients to avoid all exposure to sunlight during the 24 hours following photopheresis treatment.

CATARACT FORMATION:

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.

Instruct patients 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.

VENOUS AND ARTERIAL THROMBOEMBOLISM:

Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, have been reported with UVADEX administration through photopheresis systems for treatment of patients with graft-versus-host disease, a disease for which UVADEX is not approved.

Information for Patients:

Patients should be told emphatically to wear UVA-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SP 15 or higher) for the twenty-four (24) hour period following treatment with methoxsalen, whether exposed to direct or indirect sunlight in the open or through a window glass.

Drug Interactions:

See **Warnings** Section.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

See **Warnings** Section.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methoxsalen is administered to a nursing woman.

Pediatric Use:

Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenicity as described in the Warnings Section as well as the probability of actinic degeneration which is also described in the Warnings Section.

Patients with Renal or Hepatic Impairment

UVADEX® has not been evaluated in patients with renal or hepatic impairment

Renal impairment: Although renal transplant recipients with poor renal function have been treated with photopheresis using UVADEX®, little additional information is available on the use of UVADEX® in patients with varying degree of renal impairment. No reduction of dose or prolongation of UV light protection were reported in the renal transplant recipients who have undergone photopheresis treatment.

Hepatic impairment: No specific information is available on the use of photopheresis with UVADEX® in patients with hepatic impairment. In view of the very low systemic exposure to methoxsalen, it is unlikely that patients with severe hepatic impairment will be at greater risk than patients with normal hepatic function. However, the potential benefits of photopheresis treatment should be weighed against any possible risk before embarking on the procedure.

ADVERSE REACTIONS

Side effects of photopheresis (UVADEX® used with the THERAKOS® Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%). In study CTCL 3 (UVADEX®), 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.

POSTMARKETING: An analysis of postmarketing data shows the following events occurred with an incidence of <0.01%: rash, allergic reaction, pyrexia, nausea, dysgeusia.

OVERDOSAGE

There are no known reports of overdosage with extracorporeal administration of methoxsalen. However, in the event of overdosage, the patient should be kept in a darkened room for at least 24 hours.

DRUG DOSAGE AND ADMINISTRATION

Each UVADEX® treatment involves collection of leukocytes, photoactivation, and reinfusion of photoactivated cells. UVADEX® (methoxsalen) Sterile Solution is supplied in 10 mL vials containing 200 mcg of methoxsalen (concentration of 20 mcg/mL). The THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System Operator's Manual should be consulted before using this product. UVADEX® should not be diluted. The contents of the vial should be injected into the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System immediately after being drawn up into a syringe. Do not inject directly into patients. The UVADEX® vial is for single use only. Any UVADEX® that is not used during a procedure should be immediately discarded. UVADEX® can adsorb onto PVC and plastics, therefore only THERAKOS® UVAR XTS® or THERAKOS® CELLEX® photopheresis procedural kits supplied for use with the instrument should be used to administer this medicinal product. Once UVADEX® is drawn into a plastic syringe it should be immediately injected into the photoactivation bag. UVADEX® exposed to a plastic syringe for more than one hour should be discarded.

During treatment with the THERAKOS® UVAR XTS® or 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®

Frequency/Schedule of Treatment:

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 or 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.

HOW SUPPLIED

UVADEX® (methoxsalen) Sterile Solution 20 mcg/mL in 10 mL amber glass vials (NDC 64067-216-01), and cartons of 12 vials (NDC 64067-216-01). One vial of 10 mL contains 200 micrograms methoxsalen. The drug product must be stored between 59°F (15°C) and 86°F (30°C)

REFERENCES

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