

**ARE YOU STILL HAVING
CUTANEOUS
T-CELL
LYMPHOMA
SKIN SYMPTOMS?**

**AFTER TRYING SKIN-
DIRECTED THERAPIES**

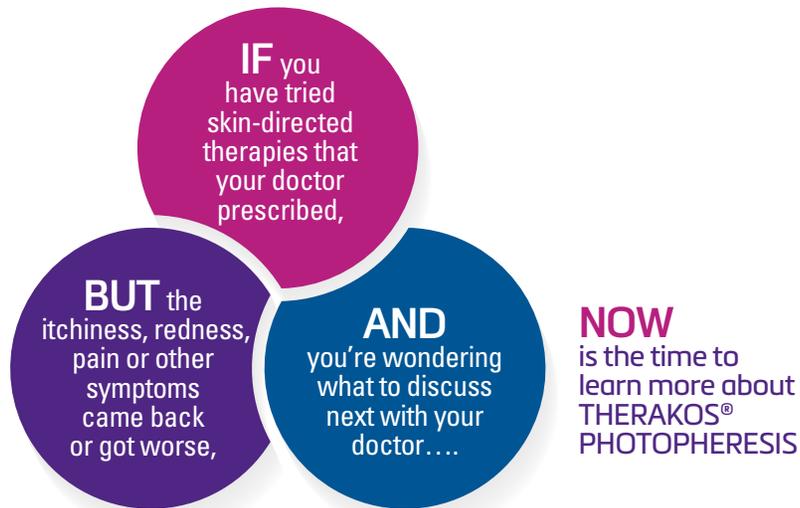
**AND YOU WONDER
WHAT TO DO NOW...**

**TALK WITH YOUR
DOCTOR ABOUT A
DIFFERENT OPTION**

People shown in pictures are not real patients or healthcare professionals.

LEARN MORE

FINDING ANOTHER WAY TO TREAT CTCL SKIN SYMPTOMS



What is the THERAKOS Photopheresis Systems Procedure?

The THERAKOS CELLEX Photopheresis System procedure is a medical procedure in which blood from a patient is collected into a specialized machine that separates the white blood cells from the other blood components. The other blood components are returned to the patient and white blood cells are then treated with UVADEX, which makes them sensitive to ultraviolet (UV) light. The treated white blood cells are exposed to UVA irradiation inside the machine, and then returned to the patient. This medical procedure is used to treat skin problems associated with CTCL in patients who have not been responsive to other forms of treatment given by their doctor.

IMPORTANT SAFETY INFORMATION

UVADEX (methoxsalen) Sterile Solution should only be used by doctors who have special skills in the diagnosis and treatment of CTCL and who have received special training and have experience in the THERAKOS CELLEX Photopheresis System.

Please see Important Safety Information on pages 10–11 and accompanying Full Prescribing Information, including the **BOXED WARNING**, for UVADEX.

LEARN MORE

IT MAY BE TIME FOR YOU AND YOUR DOCTOR TO CONSIDER A DIFFERENT TREATMENT

With your CTCL, you may need a treatment that comes at CTCL differently.

- ✓ A treatment that may help relieve your skin symptoms.
- ✓ A treatment that may help manage CTCL skin symptoms from the inside out.
- ✓ A treatment that harnesses the power of your own immune system to help treat your CTCL skin symptoms.



IMPORTANT SAFETY INFORMATION (continued)

DO NOT UNDERGO THE THERAKOS PHOTOPHERESIS SYSTEM PROCEDURE IF:

- You have a condition that makes you unable to tolerate loss of blood volume.
- You are allergic or hypersensitive to 8-methoxypsoralen, methoxsalen, or psoralen compounds.
- Your doctor has diagnosed you with a blood-clotting or bleeding problem that can lead to either a blood clot or excessive bleeding.
- You have had your spleen removed.

It is recommended that you discuss the therapy and your conditions with your doctor.



LEARN MORE

TREATING CTCL SKIN SYMPTOMS FROM THE INSIDE OUT

THERAKOS® Photopheresis is a medical therapy your doctor may recommend.

Here's what happens with THERAKOS Photopheresis

<p>01 You are connected to the THERAKOS Photopheresis instrument through an IV.</p>	<p>04 Your white blood cells are treated with UVADEX® (methoxsalen) Sterile Solution, which is activated by ultraviolet light.</p>
<p>02 A small amount of your blood is collected. Your white blood cells are then separated from your blood. They stay in the instrument to be treated.</p>	<p>05 The treated white blood cells are infused back into your body. This may help your CTCL skin symptoms.</p>
<p>03 The blood that was collected is promptly returned to your body.</p>	<p>The exact way it works is not known.</p>

IMPORTANT SAFETY INFORMATION (continued)

The information below is about the use of UVADEX® (methoxsalen) Sterile Solution with the THERAKOS CELLEX® Photopheresis System for the treatment of skin conditions associated with Cutaneous T-Cell Lymphoma (CTCL).

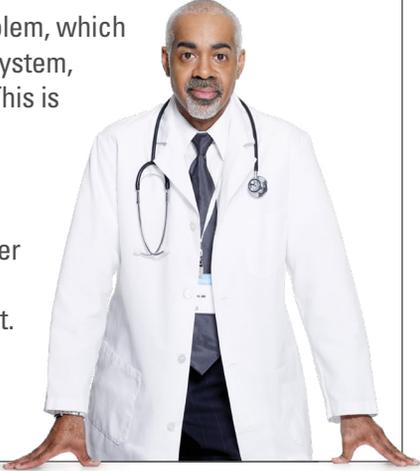
It is recommended that you discuss the therapy and your conditions with your doctor.

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LEARN MORE

TREAT YOUR CTCL SKIN SYMPTOMS FROM WITHIN

CTCL symptoms that may be bothering you appear to be outside of your body—on your skin.

	<p>So why does THERAKOS Photopheresis use blood from inside your body?</p>
<ul style="list-style-type: none"> • THERAKOS Photopheresis helps your body manage the cells involved in skin symptoms of CTCL. • Getting closer to the source of the problem, which involves your blood and your immune system, may help relieve your skin symptoms. This is the goal of THERAKOS Photopheresis. • With a little help, your body's immune system can be put to work to help you. THERAKOS Photopheresis can empower your immune system to work on your CTCL skin symptoms from the inside out. <p>NOTE: The exact way that THERAKOS Photopheresis works is not known.</p> 	

IMPORTANT SAFETY INFORMATION (continued)

What is UVADEX (methoxsalen [meth-ox-sah-len]) Sterile Solution?

UVADEX (methoxsalen) Sterile Solution is used with the THERAKOS CELLEX Photopheresis System for the treatment of skin problems associated with CTCL in patients who have not responded to other types of treatment given by their doctor.

It is recommended that you discuss the therapy and your conditions with your doctor.



TALK OPENLY

ASK YOUR DOCTOR IF THERAKOS[®] PHOTOPHERESIS IS RIGHT FOR YOU

Your conversation could go like this...

Doctor, I've tried treatments that are directed at my skin but...

My skin symptoms don't seem to be responding so...

I'm wondering if THERAKOS Photopheresis might be an option for me and...

I'd like to talk more with you about it.



IMPORTANT SAFETY INFORMATION (continued)

DO NOT USE UVADEX IF:

- You are allergic to methoxsalen, any product similar or related to it, such as psoralen, or any of the other ingredients in UVADEX.
- You have a history of a light-sensitive condition or disease.
- You have had an eye lens removed; use of UVADEX in this condition can increase the risk of retinal damage.

Please see Important Safety Information on pages 10–11 and accompanying Full Prescribing Information, including the **BOXED WARNING**, for UVADEX.

TALK OPENLY

TALK ABOUT WHAT MATTERS TO YOU

Deciding on a treatment plan involves considering:

- ✓ The current status of your CTCL
- ✓ What benefits the treatment may have
- ✓ What risks the treatment may have
- ✓ What is involved in getting the treatment
- ✓ How well the treatment fits with your daily routine
- ✓ If the treatment is right for you



Your doctor counts on you to ask questions and to talk openly about what matters to you. Your treatment is just that—*your treatment*.

So be sure to take an active role in your treatment decisions.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS

- You may be at greater risk of sun sensitivity with UVADEX. Tell your doctor if you are taking other medications that cause sensitivity to sunlight, 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.
- If you are pregnant or plan to become pregnant, tell your doctor. Methoxsalen can harm your unborn baby. Tell your doctor right away if you become pregnant during your UVADEX treatment. If you are breastfeeding or plan to breastfeed, tell your doctor. It is not known if methoxsalen passes into your breastmilk.

It is recommended that you discuss the therapy and your conditions with your doctor.



WORK TOGETHER

WORK WITH YOUR DOCTOR ON A PLAN THAT IS RIGHT FOR YOU

If you and your doctor decide that THERAKOS® Photopheresis is the right option for you, you will talk about the potential benefits and risks of treatment. This will help you be more prepared. Then you will work together to:

PICK a treatment center



from more than **200** treatment centers in North America

PLAN for each visit to be:



2 days in a row

1.5–4 hours* per treatment

PREPARE



Visits will be about **every 2–4 weeks** for a minimum of 6 months



You can read, email, watch television, or nap to pass the time

*Depending on the instrument used

IMPORTANT SAFETY INFORMATION (continued)

- After UVADEX is given, exposure to sunlight and/or ultraviolet radiation may result in premature aging of your skin.
- Let your doctor know if you currently have skin cancer or if you had skin cancer in the past.
- If you are given too much UVADEX, you may get serious burns from UVA or sunlight (even through window glass).
- Avoid exposure to sunlight during the 24 hours after treatment.
- Exposure to UVA light when UVADEX is used can cause cataract formation if proper eye protection is not used.

Please see Important Safety Information on pages 10–11 and accompanying Full Prescribing Information, including the **BOXED WARNING**, for UVADEX.

AVOID



pregnancy

The medicine used may harm an unborn child



sunlight

for 24 hours after treatment

You should avoid sunlight/sun exposure for the first 24 hours after treatment. Please discuss your sun sensitivity risks with your healthcare professional.

KNOW



Results may vary from person to person. It is not possible to predict if and how well this therapy will work for you.

Seeing results may take time and may be different for each person. Although you may see results sooner, your doctor may suggest that you give your treatment a minimum of 6 months. Your doctor will talk with you about how long your therapy should continue.



Know the potential side effects.

There are some risks. Be sure to talk with your doctor about this.



IMPORTANT SAFETY INFORMATION (continued)

- You must wear UVA light-absorbing, wrap-around sunglasses for the 24 hours after treatment with UVADEX when you are exposed to direct or indirect sunlight, whether you are outdoors or exposed through a window.
- If you are being treated for Graft vs Host Disease (GVHD), consult your physician for information regarding blood clots involving the lung and other parts of the body which have been reported in these patients. The use of UVADEX for the treatment of GVHD is not approved by the FDA.
- Safety of UVADEX in children has not been shown.

SIDE EFFECTS OF UVADEX

- Side effects of UVADEX used with the THERAKOS Photopheresis System are mainly related to low blood pressure.

It is recommended that you discuss the therapy and your conditions with your doctor.



The information below is about the use of UVADEX® (methoxsalen) Sterile Solution with the THERAKOS CELLEX® Photopheresis System for the treatment of skin conditions associated with Cutaneous T-Cell Lymphoma (CTCL).

It is recommended that you discuss the therapy and your conditions with your doctor.

What is UVADEX (methoxsalen [meth-ox-sah-len]) Sterile Solution?

UVADEX (methoxsalen) Sterile Solution is used with the THERAKOS CELLEX Photopheresis System for the treatment of skin problems associated with CTCL in patients who have not responded to other types of treatment given by their doctor.

IMPORTANT SAFETY INFORMATION

UVADEX (methoxsalen) Sterile Solution should only be used by doctors who have special skills in the diagnosis and treatment of CTCL and who have received special training and have experience in the THERAKOS CELLEX Photopheresis System.

DO NOT USE UVADEX IF:

- You are allergic to methoxsalen, any product similar or related to it, such as psoralen, or any of the other ingredients in UVADEX.
- You have a history of a light-sensitive condition or disease.
- You have had an eye lens removed; use of UVADEX in this condition can increase the risk of retinal damage.

WARNINGS

- You may be at greater risk of sun sensitivity with UVADEX. Tell your doctor if you are taking other medications that cause sensitivity to sunlight, 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.

- If you are pregnant or plan to become pregnant, tell your doctor. Methoxsalen can harm your unborn baby. Tell your doctor right away if you become pregnant during your UVADEX treatment. If you are breastfeeding or plan to breastfeed, tell your doctor. It is not known if methoxsalen passes into your breastmilk.
- After UVADEX is given, exposure to sunlight and/or ultraviolet radiation may result in premature aging of your skin.
- Let your doctor know if you currently have skin cancer or if you had skin cancer in the past.
- If you are given too much UVADEX, you may get serious burns from UVA or sunlight (even through window glass).
- Avoid exposure to sunlight during the 24 hours after treatment.
- Exposure to UVA light when UVADEX is used can cause cataract formation if proper eye protection is not used.
- You must wear UVA light-absorbing, wrap-around sunglasses for the 24 hours after treatment with UVADEX when you are exposed to direct or indirect sunlight, whether you are outdoors or exposed through a window.
- If you are being treated for Graft vs Host Disease (GVHD), consult your physician for information regarding blood clots involving the lung and other parts of the body which have been reported in these patients. The use of UVADEX for the treatment of GVHD is not approved by the FDA.
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SIDE EFFECTS OF UVADEX

- Side effects of UVADEX used with the THERAKOS Photopheresis System are mainly related to low blood pressure.

For the THERAKOS CELLEX

Photopheresis System procedure:

What is the THERAKOS Photopheresis System procedure?

The THERAKOS CELLEX Photopheresis System procedure is a medical procedure in which blood from a patient is collected into a specialized machine that separates the white blood cells from the other blood components. The other blood components are returned to the patient and white blood cells are then treated with UVADEX, which makes them sensitive to ultraviolet light. The treated white blood cells are exposed to UVA irradiation inside the machine, and then returned to the patient. This medical procedure is used to treat skin problems associated with CTCL in patients who have not been responsive to other forms of treatment given by their doctor.

DO NOT UNDERGO THE THERAKOS PHOTOPHERESIS SYSTEM PROCEDURE IF:

- You have a condition that makes you unable to tolerate loss of blood volume.
- You are allergic or hypersensitive to 8-methoxypsoralen, methoxsalen, or psoralen compounds.
- Your doctor has diagnosed you with a blood-clotting or bleeding problem that can lead to either a blood clot or excessive bleeding.
- You have had your spleen removed.

WARNINGS FOR THE THERAKOS PHOTOPHERESIS SYSTEM PROCEDURE

- Treatments with THERAKOS Photopheresis System should always be performed where standard medical emergency equipment is available.
- THERAKOS Photopheresis System procedures should not be performed

on the same day as procedures that can cause fluid changes, such as renal dialysis.

SIDE EFFECTS OF THE THERAKOS PHOTOPHERESIS SYSTEM PROCEDURE

- Low blood pressure can occur with the THERAKOS Photopheresis System procedure.
- You may get an infection and/or feel pain at the site of injection.
- Fevers of 100–102°F (37.7–38.9°C) have been seen in some patients within 6 to 8 hours after treatment. Redness of the skin may also occur with the fever.
- A decrease in red blood cells can occur if the THERAKOS Photopheresis System procedure is given too frequently. Low levels of red blood cells may cause you to feel tired.

These are not all of the possible side effects of the THERAKOS Photopheresis System procedure.

Tell your doctor about any side effects that bother you, or that do not go away. Call your doctor or pharmacist for medical advice about side effects. You may report side effects to the FDA. Call 1-800-FDA-1088 or visit www.fda.gov/medwatch. You may also report side effects by calling Mallinckrodt at 1-800-778-7898.

Please see the accompanying Full Prescribing Information, including the BOXED WARNING, for UVADEX.

TALK WITH YOUR DOCTOR
ABOUT A DIFFERENT OPTION

TO TREAT YOUR
CTCL SKIN
SYMPTOMS



 Learn more at
www.THERAKOS.com

Selected Important Safety Information

Treatments with THERAKOS Photopheresis System should always be performed where standard medical emergency equipment is available.

THERAKOS Photopheresis System procedures should not be performed on the same day as procedures that can cause fluid changes, such as renal dialysis.

Please see Important Safety Information on pages 10–11 and accompanying Full Prescribing Information, including the BOXED WARNING, for UVADEX. It is recommended that you discuss the therapy and your conditions with your doctor.



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UVADEX®

(Methoxsalen)

STERILE SOLUTION, 20 mcg/mL

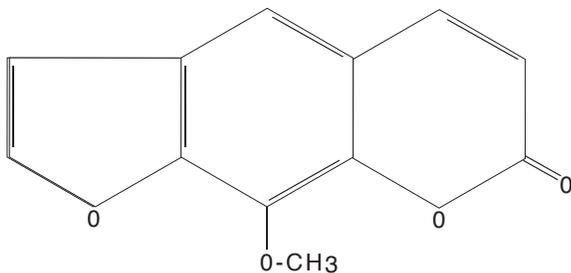
Rx ONLY.

CAUTION: READ THE 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® CELLEX® Photopheresis System. Please consult the CELLEX® 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® CELLEX® Photopheresis System 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 THERAKOS® UVAR and UVAR XTS® Photopheresis 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® 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

- 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.

Photosensitivity

Severe photosensitivity can occur in patients treated with UVADEX®. Advise patients to wear UVA absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SP 15 or higher), and avoid all exposure to sunlight for twenty-four (24) hours following photopheresis treatment. See **Precautions** section for additional information.

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 THERAKOS[®] Photopheresis Systems) 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

Adverse reactions reported from postmarketing experience include nausea, dysgeusia, photosensitivity reaction, pyrexia and hypersensitivity reactions including anaphylaxis and rash.

OVERDOSAGE

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[®] 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[®] 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[®] 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® 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 × 0.017 = mL of UVADEX®
for each treatment

Example: Treatment volume of 240 mL × 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

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling of Parenteral Antineoplastics. JAMA, 1985; 253 (11): 1590–1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426–428.
5. Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from The Mount Sinai Medical Center. CA- A Cancer Journal for Clinicians, 1983;(Sept/Oct) 258–263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin of Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990;47:1033–1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), AM J. Health-Syst Pharm, 1996; 53: 1669–1685.

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