An integrated, closed photopheresis system designed for a strategic immune response.

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.

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.

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.

Please see additional Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator's Manual.
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.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

UVADEX is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, oral 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, the patient should be advised to avoid becoming pregnant. It is not known whether this drug is excreted in human milk.

• Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient throughout the procedure and emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available for treatment.

• Procedures, such as renal dialysis, which might cause significant fluid changes (and expose the patient to potential should be advised to avoid becoming pregnant. It is not known whether this drug is excreted in human milk.

• Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair.

• 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, the patient should be advised to avoid becoming pregnant. It is not known whether this drug is excreted in human milk.

• Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient throughout the procedure and emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available for treatment.

• 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.

• Venous access carries a small risk of infection and pain.

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 (B-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 the accompanying full Prescribing Information for UVADEX. Please see also the appropriate THERAKOS Photopheresis System Operator’s Manual.

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%).
Single-Harvest, Continuous-Flow Centrifuge

- Blood separation is accomplished by the use of a custom-made continuous-flow centrifuge bowl. Centrifugal force applied to the bowl by a specially designed centrifuge separates the blood components by specific gravity.

- Separation is influenced by the speed of the centrifuge. The sensors in the centrifuge chamber and on the pump deck facilitate automatic collection of the buffy coat.

Reduced Extracorporeal Volume (ECV)

- ECV is dependent on patient hematocrit as well as the needle configuration. Nevertheless, the double-needle configuration reduces the fluid shifts to and from the patient.
  - Estimated ECV is 280 mL in a double-needle mode for a patient with a hematocrit of 40%.
  - This ECV is a 12% to 62% reduction, compared with single-needle mode, depending on the return bag threshold value.

- Whole Blood Processed, Fluid Balance, and Collect and Return Flow Rates are displayed in real time.

- For patients who require blood prime based on body weight and hematocrit, procedure is provided.

CAUTION:

In some medical conditions, the patient’s hematocrit may change from day to day. Use a hematocrit measured within 48 hours of photopheresis to estimate the THERAKOS CELLEX Photopheresis Procedural Kit ECV during a treatment.

Automated Leukocyte UVA Exposure

- Custom photoactivation time algorithm designed to ensure delivery of UVA energy to cells.

WARNING:

- The calculated dose of UVA light energy will not be delivered if the THERAKOS CELLEX Light Assembly is changed after the calculation of photoactivation MINUTES REMAINING is displayed.
- The calculated dose of UVA light energy will not be delivered if PHOTOACTIVATE is ended or aborted before the MINUTES REMAINING is equal to 0.0.

Fluid Management System

- Peristaltic Pumps (5)
- Hematocrit Sensor
- Tubing Guides
- Treatment Bag
- Collect and Return Pressure Sensors
- Centrifuge Pressure Sensor
- Air Detectors
- Return Bag
- Photoactivation Module
- Single-Harvest, Continuous-Flow Centrifuge
- Smart Card (records instrument data)

WARNING:

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.

Please see Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator’s Manual.
An Integrated, Closed Photopheresis System

Automated, Consistent, and Faster*
*Faster when compared with operation under Single-Needle Mode.

Reduced Extracorporeal Blood Volume Required
- Reduce required blood volume drawn from patient with the CELLEX® System in Double-Needle Mode

Continuous RBC Return When Used in Double-Needle Mode
- Red blood cells (RBCs) and plasma are returned continuously throughout treatment

Complete Reinfusion
- System automatically returns all treated leukocytes to the patient following photoactivation

Single-Harvest Buffy Coat
- The CELLEX® System is designed to harvest one concentrated leukocyte fraction using either continuous or discontinuous blood flow
- Automatic sensors help determine when to stop buffy coat harvest and aid in the calculation of the photoactivation time

Automated Photoactivation
- Designed to provide consistent treatment of leukocytes with continuous recirculation and calculated UVA exposure

Reduce Overall Treatment Time Using Double-Needle Mode

Single-Harvest, Continuous-Flow Centrifuge
- Maintain expanding leukocyte fraction in the centrifuge during continuous-flow separation and collect in a single harvest
- Constant spinning of the centrifuge allows clean separation and reduces overall collection time

Automatic Interface Detection
- Achieve a consistent buffy coat through Bowl Optic Sensor technology
- Optical sensor detects RBC/plasma interface, and continuous monitoring maintains interface as leukocyte fraction expands

Automatic Isolation of Treated Fraction
- Hematocrit Sensor detects the RBC concentration and stops removal of cells from the centrifuge, minimizing entrance of RBCs into the treatment bag

Calculated Treatment Dosing
- System designed to automatically calculate appropriate methoxsalen dose using treatment volume parameter

In Comparison to Single-Needle Mode, Double-Needle Mode Offers:
- Faster Collection
  - Simultaneously draw and return blood to help maximize procedural efficiency and reach whole blood processed target sooner
- Fluid Management
  - Reduce ECV with continuous blood return using double-needle mode
- Added Flexibility
  - Continuously return fluids to maintain patient’s circulating RBC volume during the procedure

WARNING:
- Single-Needle Mode is a discontinuous flow process, even though the harvesting of white blood cells in the Centrifuge Bowl is continuous. It is not possible to maintain isovolemic conditions in Single-Needle Mode. The patient must be able to tolerate the predicted procedural kit ECV without simultaneous fluid replacement

NOTE:
Carefully read the Methoxsalen (20 micrograms/mL) package insert for side effects prior to dispensing this medication.

WARNING:
Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for any signs of hypotension.

Please see Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator’s Manual.
The CELLEX® System Uses True Touch Screen Technology Designed to Provide an Accurate and Immediate Response to Your Patients' Needs

The operator interface consists of a display monitor with an integrated touch screen. The Interface displays the treatment status, treatment data, and any alarm information. You can perform all treatment operations, including PRIME, COLLECT, PHOTOACTIVATE, REINFUSE, and alarm handling by using the integrated touch screen. Visual and audible alarms are used to alert all special operating conditions.

Customized Options
- Customize treatment parameters based on initial patient assessment at the time of treatment
- Operator directs all treatment phases using versatile touch-screen keypad with 16 adjustable parameter settings
- Allows for real-time response to emerging treatment conditions

Real-Time Display
- Color LCD monitor displays real-time, informative, graphical and textual readings, including processed blood volume, collect and return rates with corresponding line pressures, and fluid balance limits

Automatic System Response
- During buffy coat harvest, operator may expand real-time hematocrit chart to monitor automatic hematocrit detection or gain assistance with manual intervention
- On-screen messages immediately display recommended corrective actions during warning-alarm notifications

Physical Instrument Specifications

<table>
<thead>
<tr>
<th>Dimensions (Height x Width x Depth)</th>
<th>Working Height</th>
<th>Weight</th>
<th>Recommended Operating Space</th>
</tr>
</thead>
<tbody>
<tr>
<td>163 cm x 58.4 cm x 79 cm (64 in x 23 in x 31 in)</td>
<td>84 cm (33 in) height from floor to pump deck surface</td>
<td>155 kg (341 lb)</td>
<td>25.4 cm (10 in) clearing on all sides</td>
</tr>
</tbody>
</table>

For further information on intended use, warnings, and limitations please refer to the operator’s manual.

NOTE:
- The operator interface displays FLUID BALANCE as fluid enters and leaves the COLLECT and RETURN Lines. It is not currently possible to reset this value at the end of a blood prime. Note the value at the time that the patient is connected and use this value as the FLUID BALANCE “zero”
- Approximately 230 mL of a packed RBC unit with a hematocrit of 57% will be required to prime the Collect Line, Centrifuge Bowl, and the Patient RETURN Line
- An additional 100 mL of volume from the packed RBC bag must be available if it is to be used during BUFFY COAT to push out the buffy coat or to re-purge the Centrifuge Bowl in a troubleshooting scenario. Diverting the prime solution to this bag will provide that volume
- Hematocrit values displayed on the Hematocrit Bar Graph and % Hematocrit Plot pertain to the hematocrit of the Treatment Volume (Buffy Coat product) and not the patient. Sample results obtained via laboratory analyzers may vary. Laboratory analyzers are calibrated to detect only levels within expected clinical low to high ranges

Please see Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator’s Manual.
A Strategic Immune Response

In patients unresponsive to other forms of treatment

THERAKOS® Photopheresis enhances the immunologic response to cutaneous T-cell lymphoma (CTCL) skin manifestations

THERAKOS Photopheresis may induce an immunomodulatory effect against CTCL skin manifestations:

- Inhibits DNA synthesis and cell division, inducing apoptosis in treated white blood cells (WBCs), including CTCL cells
- Animal studies suggest that photopheresis may activate an immune-mediated response against malignant T cells

Treatment process involves the application of UVADEX (methoxsalen) Sterile Solution outside the body:

- The patient’s blood is extracted
- WBCs are isolated and treated extracorporeally with methoxsalen
- UVADEX is photoactivated by ultraviolet light and binds to DNA in the WBCs
- The treated WBCs are then reinfused into the patient
- WBCs undergo apoptosis, which is believed to trigger an immune response against the malignant T cells which play a role in CTCL skin manifestations

An established tolerability profile:

- Adverse events (AEs) in clinical trials were primarily related to hypotension secondary to changes in extracorporeal volume (>1%)
- In Trial 3:
  - Six serious cardiovascular AEs (5 unrelated to photopheresis) were reported in 5 patients (10%)
  - Six infections were also reported in 5 patients
  - Two were Hickman catheter infections in 1 patient
- 0.01% incidence of rash, allergic reaction, pyrexia, nausea, and dysgeusia, as shown in a postmarketing data analysis

The exact mechanism of action of UVADEX is not known.

Meaningful responses, even in tough-to-treat disease:

Efficacy of THERAKOS® Photopheresis was established in 3 clinical trials (N=147)

Successful response rates demonstrated in 3 trials:

- Three multicenter, single-arm, open-label trials studied efficacy and safety. All trials enrolled CTCL patients with tough-to-treat plaque plaques, extensive plaques, and erythrodermic disease. A successful response rate was predefined as a ≥25% reduction from baseline in skin score maintained for 4 consecutive weeks
- Although the response rates with UVADEX (methoxsalen) Sterile Solution in Trial 3 and oral methoxsalen in Trial 2 were similar, the possibility that UVADEX (methoxsalen) is inferior in efficacy to oral methoxsalen cannot be excluded due to the design and size of the clinical trials

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Oral methoxsalen (N=39)</th>
<th>54%</th>
</tr>
</thead>
</table>
| Concomitant medications: Prednisone (~10 mg/day) and topical steroids permitted

<table>
<thead>
<tr>
<th>Trial 2</th>
<th>Oral methoxsalen (N=57)</th>
<th>28%</th>
</tr>
</thead>
</table>
| Concomitant medications: No restrictions

<table>
<thead>
<tr>
<th>Trial 3</th>
<th>Ex vivo UVADEX (N=51)</th>
<th>33%</th>
</tr>
</thead>
</table>
| Concomitant medications: Topical steroids (only to treat fissures on the soles of the feet/palms of the hands) permitted

*Individual results may vary. These pivotal trials were conducted with oral methoxsalen or UVADEX in conjunction with the UVAR Photopheresis System, not the CELLEX® Photopheresis System.

*Patients were permitted to receive topical and/or systemic agents in combination with THERAKOS Photopheresis.

*THERAKOS Photopheresis treatment is performed with extracorporeal photopheresis (ECP) administration of UVADEX (methoxsalen), not with oral methoxsalen.

There is no clinical evidence of additional benefit from treatment with UVADEX beyond 6 months or a different schedule.

- The higher response rate with oral methoxsalen in Trial 1 may be partly due to the administration of systemic steroids and patients receiving more ECP treatments (mean number of treatments: Trial 1=64, Trial 2=31, Trial 3=20)
- No patients with disease in the tumor phase were treated and there are no data available regarding efficacy of UVADEX in patients with disease in the tumor phase

CTCL patients should continue treatment for a minimum of 7 cycles

Please see Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator’s Manual.
An integrated, closed system for a strategic immune response

- Single-harvest, continuous-flow centrifuge
- Buffy coat is infused with UVADEX® and exposed to UVA light
- Automated leukocyte UVA exposure
- Single- or double-needle configuration: the same procedural kit allows for either configuration at any time during the treatment
- True touch screen technology designed to provide dependable accuracy and immediate response to patients' needs

References

2. UVADEX (methoxsalen) [prescribing information]. West Chester, PA: Therakos, Inc.; January 2018.

Please see Important Safety Information, including the BOXED WARNING on pages 2-3 and the accompanying full Prescribing Information for UVADEX. Please also see the appropriate THERAKOS Photopheresis System Operator's Manual.
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 furcoumarins. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Response % Within Six Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCL 3 (UVADEX®)</td>
<td>17/51 (33)</td>
</tr>
<tr>
<td>CTCL 2 (oral methoxsalen)</td>
<td>16/57 (28)</td>
</tr>
<tr>
<td>CTCL 1 (oral methoxsalen)</td>
<td>21/39 (54)</td>
</tr>
</tbody>
</table>

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 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, 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.

Pregnancy:
Pregnancy Category D. 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 Photactivation Phase using the formula:
  \[ \text{TREATMENT VOLUME} \times 0.017 = \text{mL of UVADEX}^\circ \text{ for each treatment} \]
  Example: Treatment volume of 240 mL \times 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**

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


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