

THERAKOS™ CELLEX™

Photopheresis System



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

Important Safety Information for THERAKOS™ Photopheresis Procedure

CONTRAINDICATIONS:

Certain underlying medical conditions contraindicate THERAKOS Photopheresis, including:

- Patients who cannot tolerate extracorporeal volume loss during the leukocyte enrichment phase
- Patients with coagulation disorders or who have had previous splenectomy

WARNINGS & 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.

- Thromboembolic Events: Thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in the treatment of GvHD, an indication not approved in Canada. Special attention to adequate anticoagulation is advised when treating patients with Graft versus Host Disease (GvHD).
- Concomitant Therapy: When prescribing and administering THERAKOS Photopheresis for patients receiving concomitant therapy, exercise caution when changing treatment schedules to avoid increased disease activity that may be caused by abrupt withdrawal of previous therapy.

*The exact mechanism by which extracorporeal photopheresis (ECP) exerts its clinical effect is unknown and under continual investigation.

Important Safety Information for THERAKOS™ Photopheresis Procedure (Continued)

ADVERSE REACTIONS:

- Hypotension may occur during any treatment involving extracorporeal circulation. Monitor the patient closely during the entire treatment.
- Transient pyretic reactions, 37.7-38.9°C (100-102°F), have been observed in some patients within 6-8 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 note the UVAR XTS™ system has been upgraded to the CELLEX™ system, and Mallinckrodt is no longer manufacturing or supporting UVAR XTS™ devices and kits.

Important Safety Information for UVADEX™ (methoxsalen) Sterile Solution

INDICATION:

UVADEX™ (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the 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.

UVADEX Sterile Solution is administered extracorporeally via the UVAR XTS™ or THERAKOS™ CELLEX™ Photopheresis Systems.

CAUTION: Read the UVAR XTS™ or THERAKOS™ CELLEX™ Photopheresis Systems Operator's Manual before administering the treatment. Do not inject directly into patients.

- There is no clinical evidence to show that treatment with UVADEX Sterile Solution beyond 6 months provides additional benefit if the patient has not responded within this timeframe
- There are no data available regarding the efficacy of UVADEX Sterile Solution in patients with disease in the tumor phase
- Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenicity as well as the probability of actinic degeneration

CONTRAINDICATIONS:

UVADEX Sterile Solution is contraindicated in patients:

- There is no clinical evidence to show that treatment with UVADEX Sterile Solution beyond 6 months provides additional benefit if the patient has not responded within this timeframe
- Exhibiting idiosyncratic reactions to psoralen compounds
- Possessing a specific history of a light-sensitive disease state, such as lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism
- With aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses
- With severe cardiac disease, severe anemia, white blood cell count greater than 25,000/mm³, previous splenectomy, and coagulation disorders
- With coexisting melanoma, basal cell, or squamous cell skin carcinoma

SERIOUS WARNINGS AND PRECAUTIONS:

UVADEX Sterile Solution should be administered under the supervision of a physician experienced with treatment of cutaneous T-cell lymphoma and the use of the THERAKOS™ CELLEX™ or UVAR XTS™ Photopheresis Systems.

Do not inject directly into patients. The prescribed amount of UVADEX Sterile Solution is injected into the recirculation bag prior to the photoactivation phase.

- **Carcinogenicity:** Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. Because the dose of methoxsalen with UVADEX Sterile Solution 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 Sterile Solution therapy may be lower
- **Mutagenicity:** Methoxsalen causes DNA damage, interstrand cross-links, and errors in DNA repair
- **Teratogenicity:** Methoxsalen may cause fetal harm when given to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Both men and women who are being treated with UVADEX Sterile Solutions should take adequate contraceptive precautions both during and after completion of photopheresis therapy
- **Cataractogenicity:** Patients should be told emphatically to wear UVA-absorbing, wraparound sunglasses for 24 hours after UVADEX Sterile Solution 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
- **Skin Burning:** 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 cover exposed skin or use sunblock (SPF 15 or higher) for 24 hours following treatment with methoxsalen, whether exposed to direct or indirect sunlight outdoors or through a window. Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents

FOR MORE INFORMATION:

Please consult the full product monograph for UVADEX Sterile Solution at <https://www.mallinckrodt.ca/products/therakos/> for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece, and the appropriate THERAKOS™ Photopheresis System Operator's Manual. The product monograph is also available by calling us at 1-877-566-9466.

THERAKOS™ CELLEX™ Photopheresis System

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 patient¹
 - Estimated ECV is 280 mL in a double-needle mode for a patient with a hematocrit of 40%¹
 - This ECV is a 12% to 62% reduction, compared with single-needle mode, depending on the return bag threshold value¹
- Whole Blood Processed, Fluid Balance, and Collect and Return Flow Rates are displayed in real time¹
- For patients who require blood prime based on body weight and hematocrit, procedure is provided¹

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 cells¹

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

Operator interface

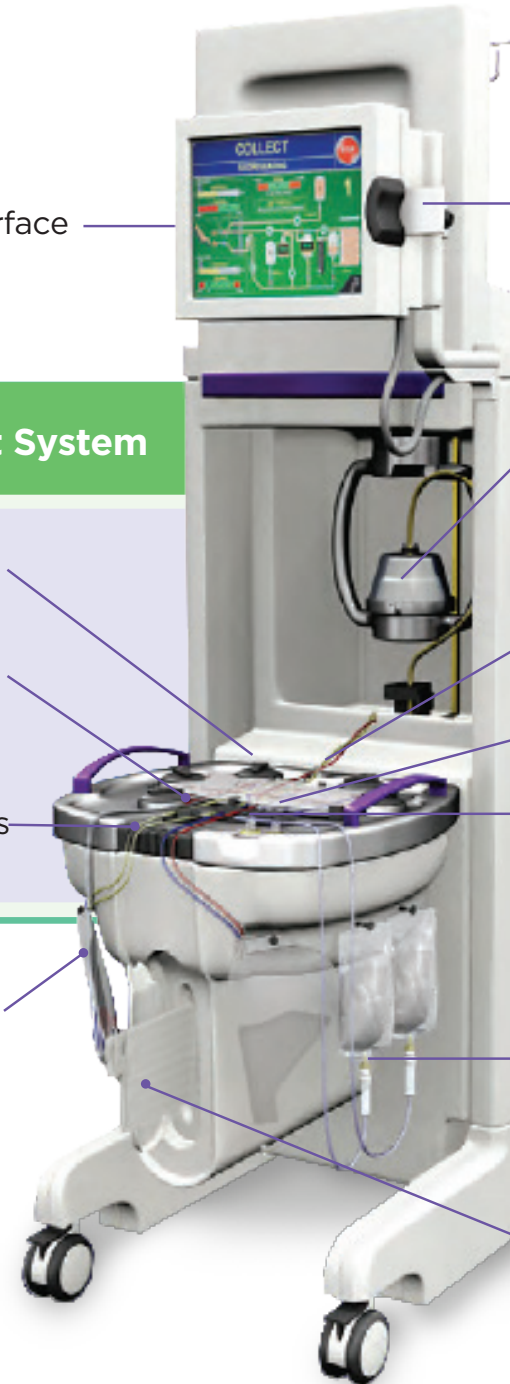
Fluid Management System

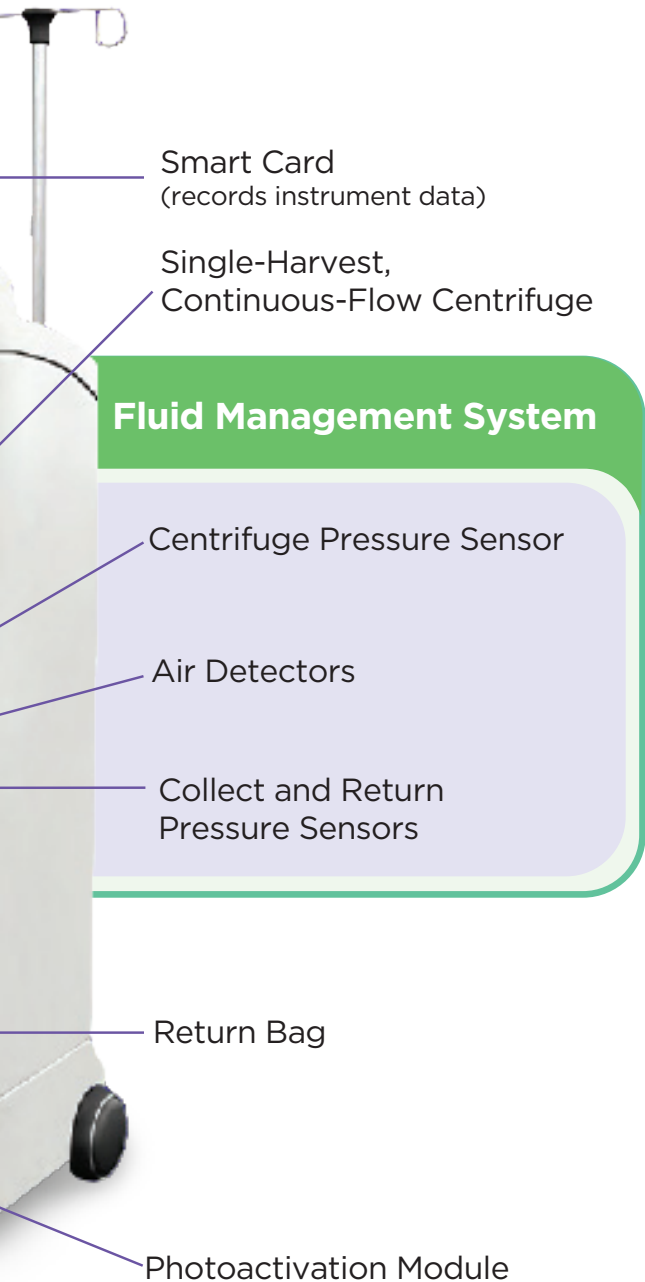
Peristaltic Pumps (5)

Hematocrit Sensor

Tubing Guides

Treatment Bag





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 gravity¹
- 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 coat¹

Flexibility in Needle Configuration

- One procedural kit allows for either single- or double-needle configuration¹
- System allows for transition to and from single- or double-needle mode during treatment to accommodate user and patient needs¹

WARNING/PRECAUTION:

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 safety information on pages 2-3 and consult the full product monograph for UVADEX Sterile Solution at <https://www.mallinckrodt.ca/products/therakos/> for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece, and the appropriate THERAKOS™ Photopheresis™ System Operator's Manual. The product monograph is also available by calling us at 1-877-566-9466.

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 Mode¹

Continuous RBC Return When Used in Double-Needle Mode

- Red blood cells (RBCs) and plasma are returned continuously throughout treatment¹

Complete Reinfusion

- System automatically returns all treated leukocytes to the patient following photoactivation¹



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

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 harvest¹
- Constant spinning of the centrifuge allows clean separation and reduces overall collection time¹

Automatic Interface Detection

- Achieve a consistent buffy coat through Bowl Optic Sensor technology¹
- Optical sensor detects RBC/plasma interface, and continuous monitoring maintains interface as leukocyte fraction expands¹

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 bag¹

Calculated Treatment Dosing

- System designed to automatically calculate appropriate methoxsalen dose using treatment volume parameter¹

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 sooner¹

Fluid Management

- Reduce ECV with continuous blood return using double-needle mode¹

Added Flexibility

- Continuously return fluids to maintain patient's circulating RBC volume during the procedure¹

- Whole Blood
- Red Blood Cells
- Plasma
- Leukocytes

NOTE:

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

WARNING:

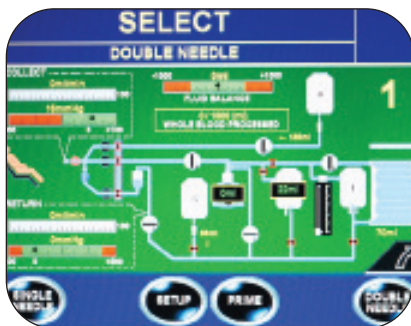
Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for any signs of hypotension.

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User-Friendly Operator Interface

The CELLEX™ System Uses True Touch Screen Technology Designed to Provide an Accurate and Immediate Response to Your Patients' Needs¹

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.¹



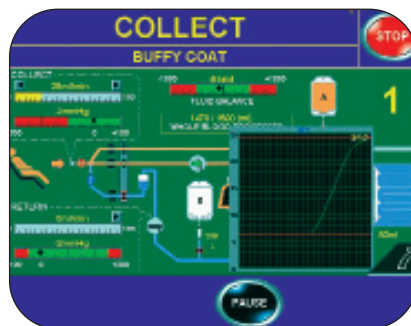
Customized Options

- Customize treatment parameters based on initial patient assessment at the time of treatment¹
- Operator directs all treatment phases using versatile touch screen keypad with multiple adjustable parameter settings¹
- Allows for real-time response to emerging treatment conditions¹



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 limits¹



Automatic System Response

- During buffy coat harvest, operator may expand real-time hematocrit chart to monitor automatic hematocrit detection or gain assistance with manual intervention¹
- On-screen messages immediately display recommended corrective actions during warning-alarm notifications¹

Physical Instrument Specifications¹

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

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

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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^{2*}

- Inhibits DNA synthesis and cell division, inducing apoptosis in treated white blood cells (WBCs), including CTCL cells²⁻⁴

Treatment process involves the application of UVADEX™ (methoxsalen) Sterile Solution outside the body²

- 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^{2,5}

An established tolerability profile

- Adverse events (AEs) in clinical trials were primarily related to hypotension secondary to changes in extracorporeal volume (>1%)²
- In Trial 3:
 - Six serious cardiovascular AEs (5 unrelated to photopheresis) were reported in 5 patients (10%)²
 - Six infections were also reported in 5 patients²
 - Two were Hickman catheter infections in 1 patient²
- The most common post-marketing events reported with UVADEX™/extracorporeal photopheresis (ECP) treatment regardless of causality assessment were obtained from spontaneous reports, clinical studies or literature and include taste perversions, vasovagal attack/fainting/dizziness, sepsis/line sepsis, anemia, hypotension, and nausea²

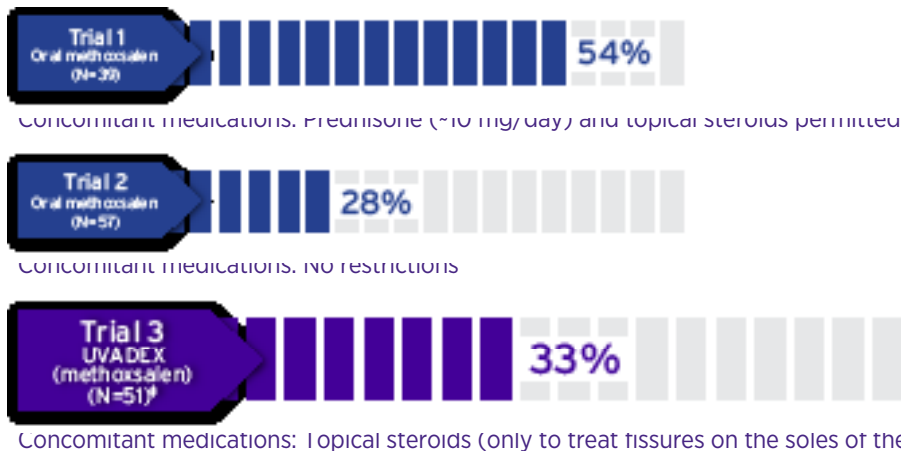
*The exact mechanism of action of UVADEX is not known.

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

Efficacy of THERAKOS™ Photopheresis was established in 3 clinical trials (N=147)²

Successful response rates demonstrated in 3 trials^{2*}



*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.²

[‡]THERAKOS Photopheresis treatment is performed with ECP administration of UVADEX (methoxsalen), not with oral methoxsalen.

- Three multicenter, single-arm, open-label trials studied efficacy and safety. All trials enrolled CTCL patients with tough-to-treat patch plaques, extensive plaques, and erythrodermic disease. A successful response rate was predefined as a $\geq 25\%$ reduction from baseline in skin score maintained for 4 consecutive weeks²
- 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 trials²
- 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)²
- 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 phase²

CTCL patients should continue treatment for a minimum of 7 cycles

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

THERAKOS™ CELLEX™ Photopheresis System

An integrated, closed system for a strategic immune response

- Single-harvest, continuous-flow centrifuge¹
- Buffy coat is infused with UVADEX™ and exposed to UVA light¹
- Automated leukocyte UVA exposure¹
- Single- or double-needle configuration: the same procedural kit allows for either configuration at any time during the treatment¹
- True touch screen technology designed to provide dependable accuracy and immediate response to patients' needs¹



References

1. THERAKOS™ CELLEX™ Photopheresis System Operator's Manual Rev. 4.0-1460451. Therakos, Inc.; 2010.
2. UVADEX (methoxsalen) Product Monograph. West Chester, PA, USA: Therakos, Inc.; May 2013.
3. Yoo EK, Rook AH, Elenitsas R, Gasparro FP, Vowels BR. Apoptosis induction of ultraviolet light A and photochemotherapy in cutaneous T-cell lymphoma: relevance to mechanism of therapeutic action. *J Invest Dermatol.* 1996;107(2):235-242.
4. Gerber A, Bohne M, Rasch J, Struy H, Ansorge S, Gollnick H. Investigation of annexin V binding to lymphocytes after extracorporeal photoimmunotherapy as an early marker of apoptosis. *Dermatology.* 2000;201(2):111-117.
5. Hwang ST, Janik JE, Jaffe ES, Wilson WH. Mycosis fungoides and Sézary syndrome. *Lancet.* 2008;371(9616):945-957.

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