THERAKOS™ CELLEX™ Photopheresis System

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

Important Safety Information for UVADEX™

INDICATION

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

- There is no clinical evidence to show that treatment with UVADEX beyond six months provides additional benefit if the patient has not responded within this timeframe.
- Not authorized for pediatric or geriatric use.

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

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

CONTRAINDICATIONS

UVADEX is contraindicated in patients:

- Hypersensitive to this drug or any ingredient in the formulation
- 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

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SERIOUS WARNINGS AND PRECAUTIONS

Carcinogenicity: Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. 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

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. Both men and women who are being treated with UVADEX 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 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.

IMPORTANT SAFETY INFORMATION FOR THERAKOS® PHOTOPHERESIS PROCEDURE

INDICATION:

The THERAKOS® CELLEX® Photophoresis System is used for the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) and systemic sclerosis (SSc). Only health care professionals with training in Therakos® Photopheresis should administer this therapy.

CONTRAINDICTIONS

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.

ADVERSE REACTIONS

Hypotension may occur during any treatment involving extracorporeal circulation. Monitor the patient closely during the entire treatment.

Transient pyretic reactions, 37.7-38.9º C (100-102º 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.

FOR MORE INFORMATION

Please consult the full product monograph for UVADEX 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.

Automated, Consistent, and Faster*

*Faster when compared with operation under Single-Needle Mode.

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[1]
  - 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 value[1]
- Whole Blood Processed, Fluid Balance, and Collect and Return Flow Rates are displayed in real time[1]
- For patients who require blood prime based on body weight and hematocrit, procedure is provided[1]

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 algorithmdesigned to ensure delivery of UVA energy to cells[1]

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

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[1]
- 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[1]

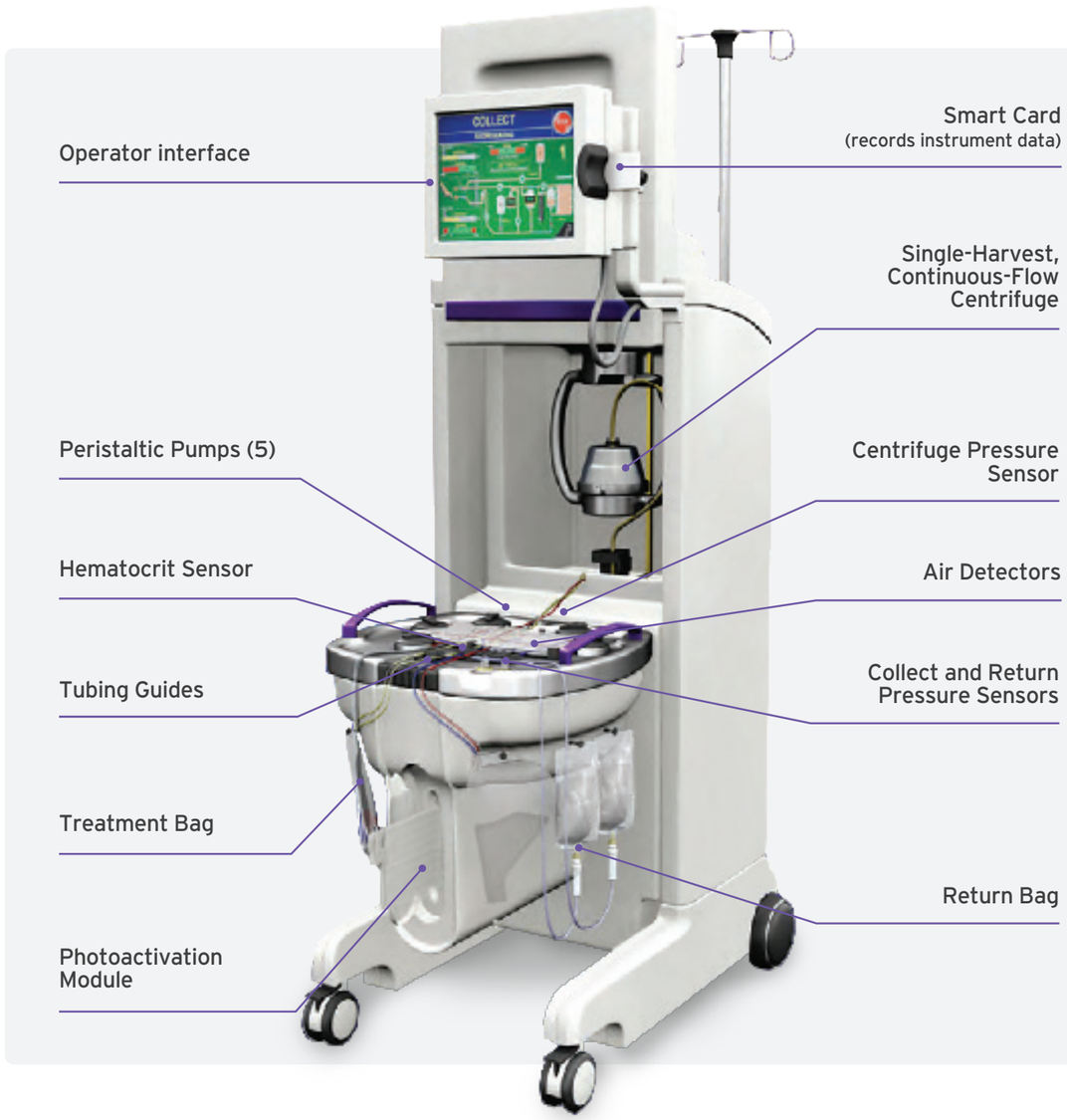
FLEXIBILITY IN NEEDLE CONFIGURATION

- One procedural kit allows for either single- or double-needle configuration[1]
- System allows for transition to and from single- or double-needle mode during treatment to accommodate user and patient needs[1]

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.

FLUID MANAGEMENT SYSTEM



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.

Automated, Consistent, and Faster*

*Faster when compared with operation under Single-Needle Mode.

Reduced Extracorporeal Blood Volume Required

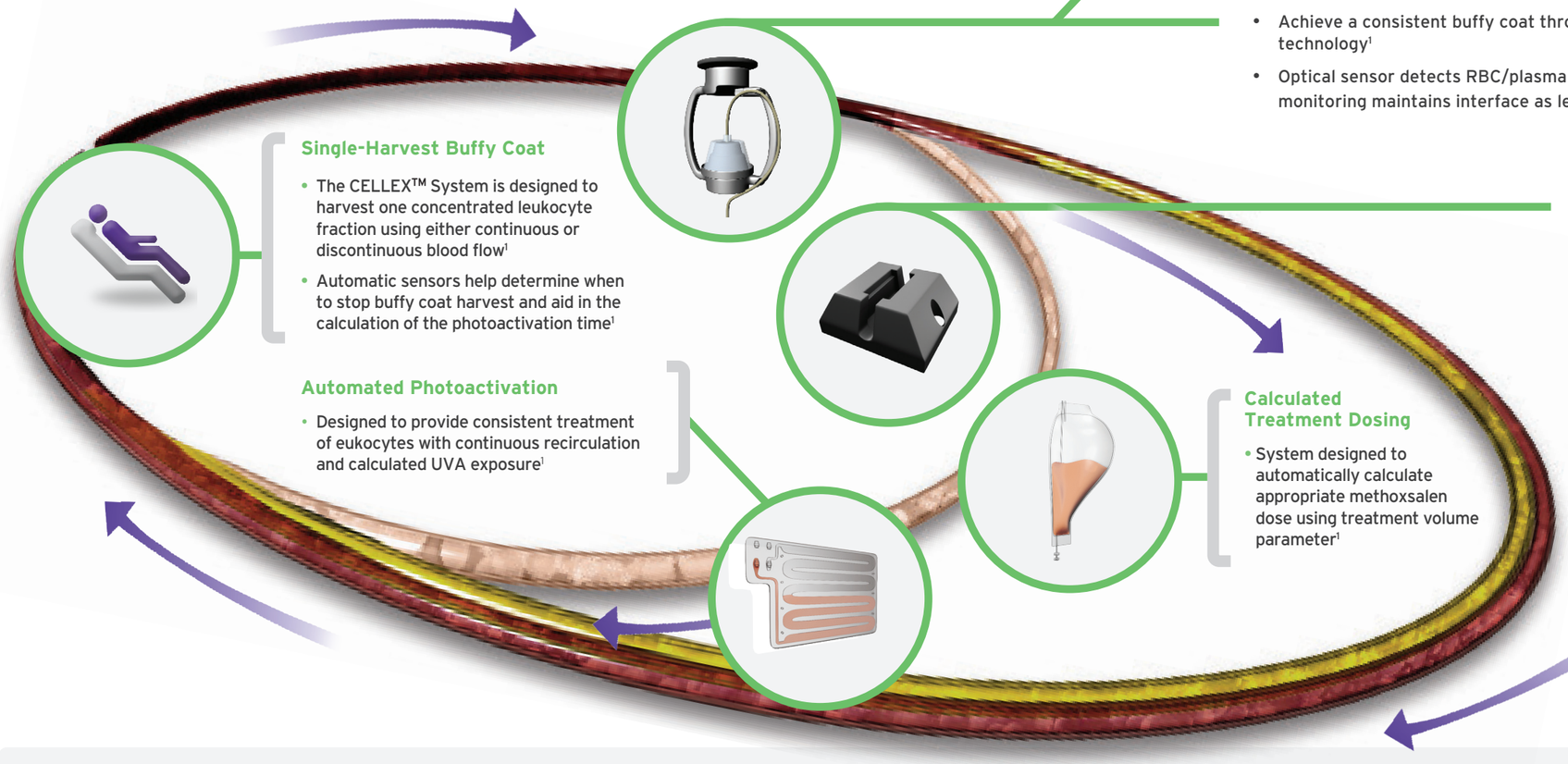
- Reduce required blood volume drawn from patient with the CELLEX™ System in Double-Needle Mode[1]

Continuous RBC Return When Used in Double-Needle Mode

- Red blood cells (RBCs) and plasma are returned continuously throughout treatment[1]

Complete Reinfusion

- System automatically returns all treated leukocytes to the patient following photoactivation[1]



Single-Harvest Buffy Coat

- The CELLEX™ System is designed to harvest one concentrated leukocyte fraction using either continuous or discontinuous blood flow[1]
- Automatic sensors help determine when to stop buffy coat harvest and aid in the calculation of the photoactivation time[1]

Automated Photoactivation

- Designed to provide consistent treatment of eukocytes with continuous recirculation and calculated UVA exposure[1]

Calculated Treatment Dosing

- System designed to automatically calculate appropriate methoxsalen dose using treatment volume parameter[1]

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[1]
- Constant spinning of the centrifuge allows clean separation and reduces overall collection time[1]

Automatic Interface Detection

- Achieve a consistent buffy coat through Bowl Optic Sensor technology[1]
- Optical sensor detects RBC/plasma interface, and continuous monitoring maintains interface as leukocyte fraction expands[1]

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[1]

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[1]

Fluid Management

- Reduce ECV with continuous blood return using double-needle mode[1]

Added Flexibility

- Continuously return fluids to maintain patient's circulating RBC volume during the procedure[1]

- Whole Blood
- Red Blood Cells
- Plasma
- Leukocytes

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:

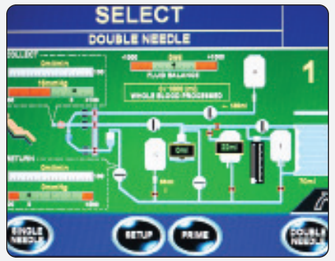
Carefully read the Methoxsalen (20 micrograms/mL) package insert for side effects prior to dispensing this medication.

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 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.

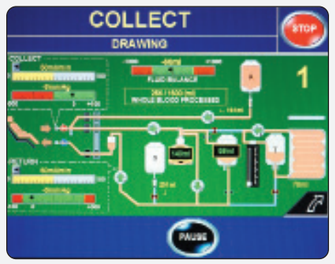
THE CELLEX™ SYSTEM USES TRUE TOUCH SCREEN TECHNOLOGY DESIGNED TO PROVIDE AN ACCURATE AND IMMEDIATE RESPONSE TO YOUR PATIENTS' NEEDS[1]

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]



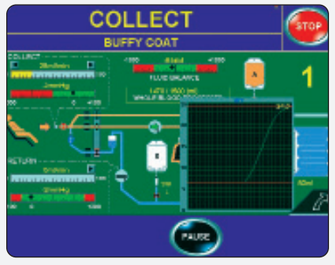
Customized Options

- Customize treatment parameters based on initial patient assessment at the time of treatment[1]
- Operator directs all treatment phases using versatile touch screen keypad with multiple adjustable parameter settings[1]
- Allows for real-time response to emerging treatment conditions[1]



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[1]



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[1]
- On-screen messages immediately display recommended corrective actions during warning-alarm notifications[1]

PHYSICAL INSTRUMENT SPECIFICATIONS[1]

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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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 cells[2-4]

Treatment process involves the application of UVADEX™ (methoxsalen) Sterile Solution outside the body[2]

- 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 patients[2]
  - Two were Hickman catheter infections in 1 patient[2]
- 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 nausea[2]

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

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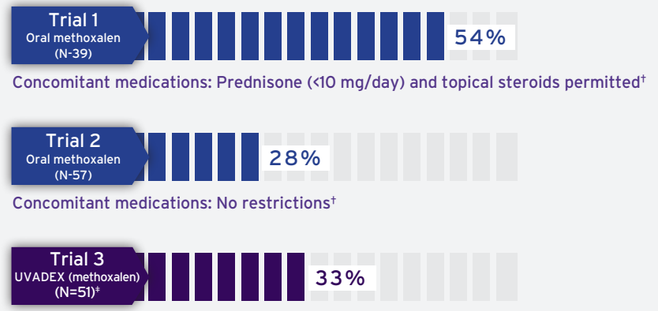
MEANINGFUL RESPONSES, EVEN IN TOUGH-TO-TREAT DISEASE*

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 methoxalen 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 ≥25% reduction from baseline in skin score maintained for 4 consecutive weeks[2]
- 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[2]
- 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 phase[2]

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 centrifuge[1]
- Buffy coat is infused with UVADEX™ and exposed to UVA light[1]
- Automated leukocyte UVA exposure[1]
- Single- or double-needle configuration: the same procedural kit allows for either configuration at any time during the treatment[1]
- True touch screen technology designed to provide dependable accuracy and immediate response to patients' needs[1]

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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