Therakos CellEx®
PHOTOPHERESIS SYSTEM

EXPERIENCE THE

THERAKOS® CELLEX® Photopheresis System

For the THERAKOS® CELLEX® Photopheresis Procedure:

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

The THERAKOS CELLEX Photopheresis System is 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

Please see additional Important Safety Information on the next page. Please also see Full Prescribing Information, including the BOXED WARNING for UVADEX® (methoxsalen), and see the THERAKOS Photopheresis System Operator's Manual.

Important Safety Information (cont'd)

For the THERAKOS® CELLEX® Photopheresis Procedure:
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

SELECT SAFETY INFORMATION FOR OPERATING THERAKOS CELLEX

For complete instructions, warnings, and precautionary information, consult the THERAKOS CELLEX Photopheresis System Operator's Manual.

WARNINGS AND PRECAUTIONS

- In consultation with the clinician, assess the patient's overall health status immediately before beginning a treatment to determine if the patient is able to tolerate the anticipated fluid shifts during the treatment. Do not proceed if the patient is unstable
- The operator must be present to supervise the treatment at all times. The operator's primary responsibility during the entire treatment is the patient's safety. Carefully monitor the patient for tolerance to the extracorporeal fluid shifts, access performance and potential allergic reactions or potential adverse events
- Throughout the treatment, you should visually monitor the instrument to confirm whole blood separation; the correct position for the plasma/red blood cell interface; unusual conditions such as hemolysis, high bilirubin and/or lipids; and unexpected fluid leaks
- Ensure settable alarm limits are appropriate for patient conditions
- AABB guidelines recommend that the temporary extracorporeal blood volume be less than or equal to 15% of the patient's Total Blood Volume. The patient's clinical condition at the time of THERAKOS Photopheresis may warrant an extracorporeal blood volume of less than 15% of Total Blood Volume to maintain hemodynamic stability. Complete assessment of the patient prior to every treatment is necessary to determine the appropriate extracorporeal blood volume and fluid balance during each treatment
- In some medical conditions, the patient's hematocrit may change from day to day. Use a hematocrit measured within 48 hours prior to photopheresis to estimate the THERAKOS CELLEX Photopheresis Procedural Kit extracorporeal volume during a treatment
- DOUBLE NEEDLE mode is required when: isovolemic FLUID BALANCE is required, minimum fluid deficit is required, minimum ECV is allowed, BLOOD PRIME is required
- 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 extracorporeal volume without simultaneous fluid replacement

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.

IMPORTANT SAFETY INFORMATION

CAUTION: READ THE THERAKOS CELLEX PHOTOPHERESIS SYSTEM'S 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.

CONTRAINDICATIONS

UVADEX is contraindicated in:

- Patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, other psoralen compounds, or any of the excipients
- Patients possessing a specific history of a light-sensitive disease state, including lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism
- Patients with aphakia because of significantly increased risk of retinal damage
- Patients that have 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. Women of childbearing potential should be advised to avoid becoming pregnant. 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
- 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 (SPF 15 or higher), and avoid all exposure to sunlight for twenty-four (24) hours following photopheresis treatment
- After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin
- Since oral psoralens may increase the risk of skin cancers, monitor closely those patients who exhibit multiple basal cell carcinomas or who have a history of basal cell carcinomas
- Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions are not followed
- Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity
- Safety in children has not been established
- Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, have been reported with UVADEX administration through photopheresis systems for treatment of patients with graft-versus-host disease, a disease for which UVADEX is not approved

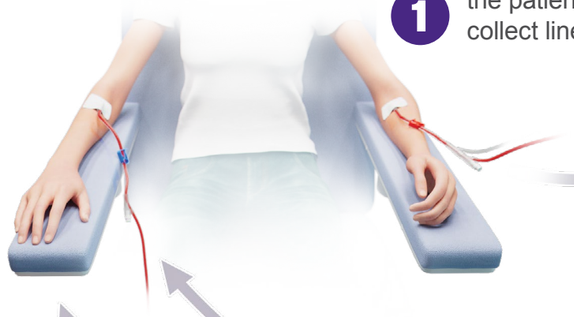
ADVERSE REACTIONS

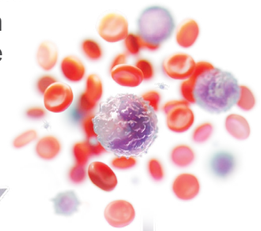
- Side effects of photopheresis (UVADEX used with the THERAKOS Photopheresis Systems) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%)

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

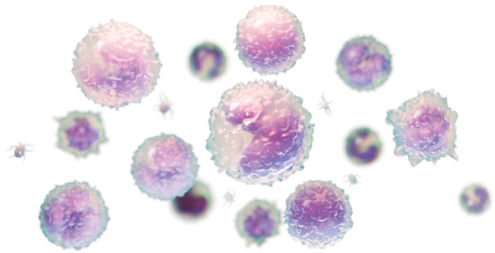
Procedure and mechanism of action

1 A small fraction of whole blood is collected from the patient through the collect line.[1]





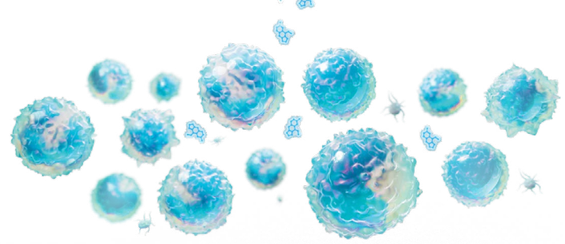
CENTRIFUGATION IN THE BOWL[1]

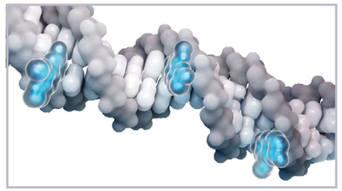


Buffy coat isolated (leukocytes and platelets)

2 With the help of the bowl optic sensor, the collection and control software, and the hematocrit sensor, the buffy coat is isolated following centrifugation, while the remaining red blood cells and plasma are returned.[1,2]

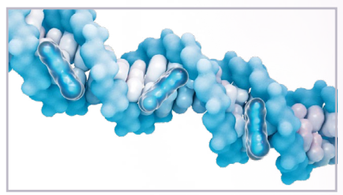
UVADEX® (methoxsalen)



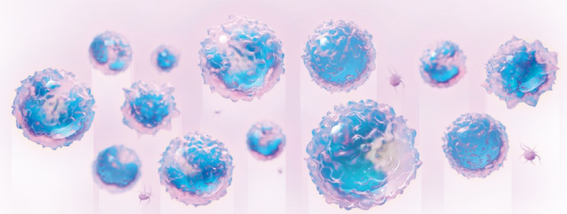


UVADEX DNA intercalation

3 The buffy coat is transferred to the treatment bag where it is then treated with UVADEX® Sterile Solution, a photosensitizing agent.[1,3-5]

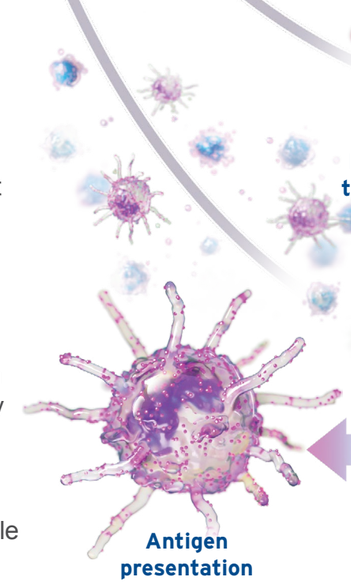


UVADEX DNA cross-links

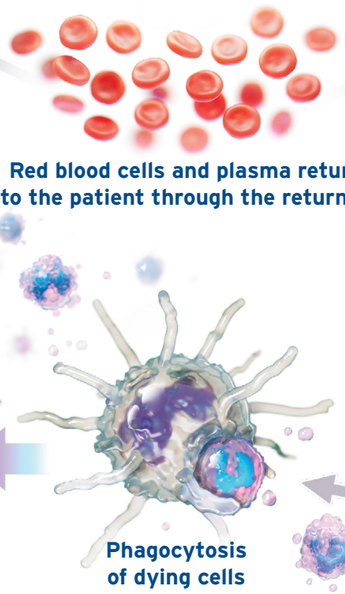


4 As the buffy coat circulates through the photoactivation module, UVADEX is photoactivated by UVA light, which triggers cell death.[1,6,7]

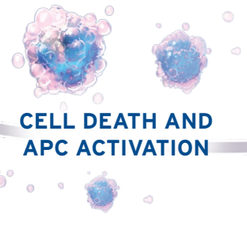
5 Antigen-presenting cells (APCs) are activated and start phagocytosing dying lymphocytes.[8-10]



Antigen presentation

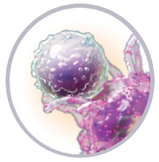


Phagocytosis of dying cells



CELL DEATH AND APC ACTIVATION

6 Once photoactivation is complete, the buffy coat (now containing living, dead, or dying cells, subcellular fragments, and soluble factors) is returned to the patient's bloodstream through the return line.[1]



7 **T-cell activation**

Translational studies suggest that Photopheresis may activate an immune-mediated response against the malignant T cells.[11,12]

Red blood cells and plasma returned to the patient through the return line[1]

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

While much is known about the mechanism of action, the exact mechanism of action is currently being studied.

The procedure pictured above illustrates a patient using double-needle mode.[1]

UVA, ultraviolet A.

The THERAKOS® CELLEX® Photopheresis System is a fully integrated, closed-loop device[1]

- Single, uninterrupted sterile fluid path to reduce the risk of cross-contamination and infection[1,13-15]
- One kit for all procedures (single-needle or double-needle mode)[1]
- Single-operator management[1,13]

DEVICE SPECIFICATIONS[1]

Dimensions (Height x Width x Depth)	163 cm x 58.4 cm x 79 cm (64 in x 23 in x 31 in)
Working Height	84 cm (33 in) from floor to pump deck surface
Weight	166 kg (366 lb)
Recommended Operating Space	50 cm (18 in) clearing on all sides
Electrical	Frequency: 50/60 Hz Nominal Voltages: 100, 115, 230, 240 volts AC power (±10%, respectively) Current: 7, 6.3, 3.9, 3.8 amps, respectively
Room Operating Temperature	15°C–27.5°C (59°F–81°F) BTU/hour: 2390
Operating Humidity	10%–75% relative humidity, non-condensing
Full Mobility	Enabling use in both inpatient and outpatient settings
Single-Use Procedural Kits*	A preconnected and sterile unit for easy setup and minimal waste Kit dimensions: 59.7 cm x 36.2 cm x 13.7 cm (23.5 in x 14.25 in x 5.38 in) Case dimensions: 61 cm x 37.4 cm x 42 cm (24 in x 14.74 in x 16.5 in; 3 kits per case) *Additional ancillary supplies including saline and anticoagulant are required to perform the procedure.

Key device components and features

OPERATOR INTERFACE[1]

Displays treatment status, treatment data, and any alarm information.

Key device components

- Integrated touch screen (where treatment operations and alarms are managed)
- Smart Card (records treatment data from each treatment for diagnostic use)

Important features

An intelligent and prioritized alarm system

- Alarms are numbered for quick reference, and each has a pop-up message, alert, and recommended action
- 3 types of alarm signals: LOW Priority, MEDIUM Priority (Operator Correctable), and MEDIUM Priority (Technical)

PHOTOACTIVATION & REINFUSION[1]

Following the addition of UVADEX® (methoxsalen), the leukocyte-enriched blood fraction is exposed to a prescribed amount of UVA light and subsequently returned to the patient.

Key device components

- Photoactivation module
- Treatment bag
- Return bag

Important features

Automated UVADEX dosage calculation

- Helps minimize dosage errors

Specific algorithm for consistent UVA irradiation

- Photoactivation time automatically calculated and set according to remaining lamp life time, percentage of hematocrit of the leukocyte-enriched blood fraction, and treatment volume

FLUID MANAGEMENT SYSTEM[1]

Controls all pump and valve functions, directs fluid routing through the Pump Tubing Organizer (where whole blood, saline, and anticoagulant are routed), and maintains flow rates during all phases of the treatment.

Key device components

- Single-harvest, continuous-flow centrifuge
- Peristaltic pumps (5)
- Tubing guides
- Centrifuge bowl pressure sensor
- Air detectors
- Collect and return pressure sensors

Important features

Built-in fluid balance calculator

- Helps estimate blood volume and set fluid balance limits prior to the procedure
- "Whole Blood Processed" and "Fluid Balance" are displayed in real time

Extracorporeal volume is dependent on patient hematocrit as well as the needle configuration.

Centrifuge bowl optic sensor technology

- Features innovative software-directed pumping mechanisms
- Delivers a consistent buffy coat by automatically identifying red cell layer and can adjust the cell separation process to help compensate for abnormal plasma conditions

Hematocrit sensor technology

- Automatically determines when buffy coat collection should end

Automatic interface and isolation of treated fraction

- Centrifuge separation for precision based on individual component mass
- Clean separation with constant centrifuge spinning

Automated collect and return flow rates

- May reduce pressure alarms and the associated treatment interruptions
- Decreases the need for operator interventions

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

Click or scan here to watch the procedural video

Patient management

The THERAKOS® CELLEX® Photopheresis System is adaptable based on physiologic and medical considerations

Vascular access

The system offers a choice of single-needle (SNM) or double-needle mode (DNM) and the ability to switch between the two according to venous access conditions.[1,14] Flexible configuration allows operators to adjust smoothly to **individual vascular access needs** in real time.[1]

- **With DNM, extracorporeal volume is reduced** compared with SNM, and the continuous fluid return may reduce treatment time[1]

The option to use DNM is dependent on vascular access and other patient factors, such as hematocrit.

Hemodynamic instability and low body weight

Blood priming and reduced extracorporeal volume using DNM enable treatment of **patients with low body weight and hemodynamic instability.**[1]

No lower limit for leukocyte levels

Regardless of the needle mode, centrifuge bowl continuously harvests 1 concentrated buffy coat.[1]

Abnormal lipid and bilirubin in plasma

Bowl optic sensor allows customization of the system to the needs of patients with **abnormal plasma conditions,** such as lipemia or hyperbilirubinemia.[1]

Reduced flow rates

Collect, return, and reinfusion flow rate limits may be adjusted for patients with **medical conditions warranting lower flow rates,** such as cardiac, renal, or pulmonary insufficiency, diabetes, hypertension, hypotension, edema, low body weight, or fragile veins.[1]

On average, the total treatment time* with the CELLEX system is 99.27 minutes.[16]

*Accounts for the buffy coat collection and handling time, the irradiation time, and the handling time after treatment.[16]

Dedicated support with the THERAKOS® CELLEX® Photopheresis System

ON-DEMAND SUPPORT AVAILABLE WHEN YOU NEED IT

Customer Care available at 1-833-223-4327

Therakos Institute, which offers training programs and educational activities for practitioners

MyTherakos, which supplies product, training, and educational materials at your fingertips

Educational materials for your patients and practice

ONGOING SUPPORT FROM OUR INTERNAL TEAM

Field engineers provide timely device support and expertise

Clinical specialists deliver personalized operator training

Product support specialists provide remote operator assistance and access to product information

Business managers offer dedicated product information and support

References: 1. THERAKOS® CELLEX® Photopheresis System Operator's Manual. **2.** Cho A, Jantschitsch C, Knobler R. Extracorporeal photopheresis–an overview. *Front Med (Lausanne).* 2018;5:236. doi:10.3389/fmed.2018.00236 **3.** UVADEX® (methoxsalen) Sterile Solution [prescribing information]. Therakos, Inc. **4.** Smith SI, Brodbelt JS. Rapid characterization of cross-links, mono-adducts, and non-covalent binding of psoralens to deoxyoligonucleotides by LC-UV/ESI-MS and IRMPD mass spectrometry. *Analyst.* 2010;135(5):943-952. **5.** Gasparro FP, Chan G, Edelson RL. Phototherapy and photopharmacology. *Yale J Biol Med.* 1985;58(6):519-534. **6.** Bladon J, Taylor PC. Extracorporeal photopheresis induces apoptosis in the lymphocytes of cutaneous T-cell lymphoma and graft-versus-host disease patients. *Br J Haematol.* 1999;107(4):707-711. doi:10.1046/j.1365-2141.1999.01773.x **7.** Tatsuno K, Yamazaki T, Hanlon D, et al. Extracorporeal photochemotherapy induces bona fide immunogenic cell death. *Cell Death Dis.* 2019;10(8):578. doi:10.1038/s41419-019-1819-3 **8.** Berger CL, Xu AL, Hanlon D, et al. Induction of human tumor-loaded dendritic cells. *Int J Cancer.* 2001;91(4):438-447. doi:10.1002/1097-0215(200002)9999:9999<::aid-ijc1073>3.0.co;2-r **9.** Huang MN, Nicholson LT, Batich KA, et al. Antigen-loaded monocyte administration induces potent therapeutic antitumor T cell responses. *J Clin Invest.* 2020;130(2):774-788. doi:10.1172/JCI128267 **10.** Bladon J, Taylor PC. Photopheresis up-regulates CD36 on monocytes and reduces CD25(+) and CD28(+) T cell numbers. *Photodiagnosis Photodyn Ther.* 2005;2(2):119-127. doi:10.1016/S1572-1000(05)00034-7 **11.** Shiue LH, Couturier J, Lewis DE, Wei C, Ni S, Duvic M. The effect of extracorporeal photopheresis alone or in combination therapy on circulating CD4(+) Foxp3(+) CD25(-) T cells in patients with leukemic cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed.* 2015;31(4):184-194. doi:10.1111/phpp.12175 **12.** Quaglino P, Comessatti A, Ponti R, et al. Reciprocal modulation of circulating CD4+CD25+bright T cells induced by extracorporeal photochemotherapy in cutaneous T-cell lymphoma and chronic graft-versus-host-disease patients. *Int J Immunopathol Pharmacol.* 2009;22(2):353-362. doi:10.1177/039463200902200212 **13.** Knobler R, Arenberger P, Arun A, et al. European dermatology forum: updated guidelines on the use of extracorporeal photopheresis 2020: part 1. *J Eur Acad Dermatol Venereol.* 2020;34(12):2693-2716. doi:10.1111/jdv.16890 **14.** Bisaccia E, Vonderheid EC, Geskin L. Safety of a new, single, integrated, closed photopheresis system in patients with cutaneous T-cell lymphoma. *Br J Dermatol.* 2009;161(1):167-169. doi:10.1111/j.1365-2133.2009.09081.x **15.** Perotti C, Sniecinski I. A concise review on extracorporeal photochemotherapy: where we began and where we are now and where are we going! *Transfus Apher Sci.* 2015;52(3):360-368. doi:10.1016/j.transci.2015.04.011 **16.** Mayer W, Kontekakis A, Maas C, Kuchenbecker U, Behlke S, Schennach H. Comparison of procedure times and collection efficiencies using integrated and multistep nonintegrated procedures for extracorporeal photopheresis. *J Clin Apher.* 2022;37(4):332-339. doi:10.1002/jca.21974

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