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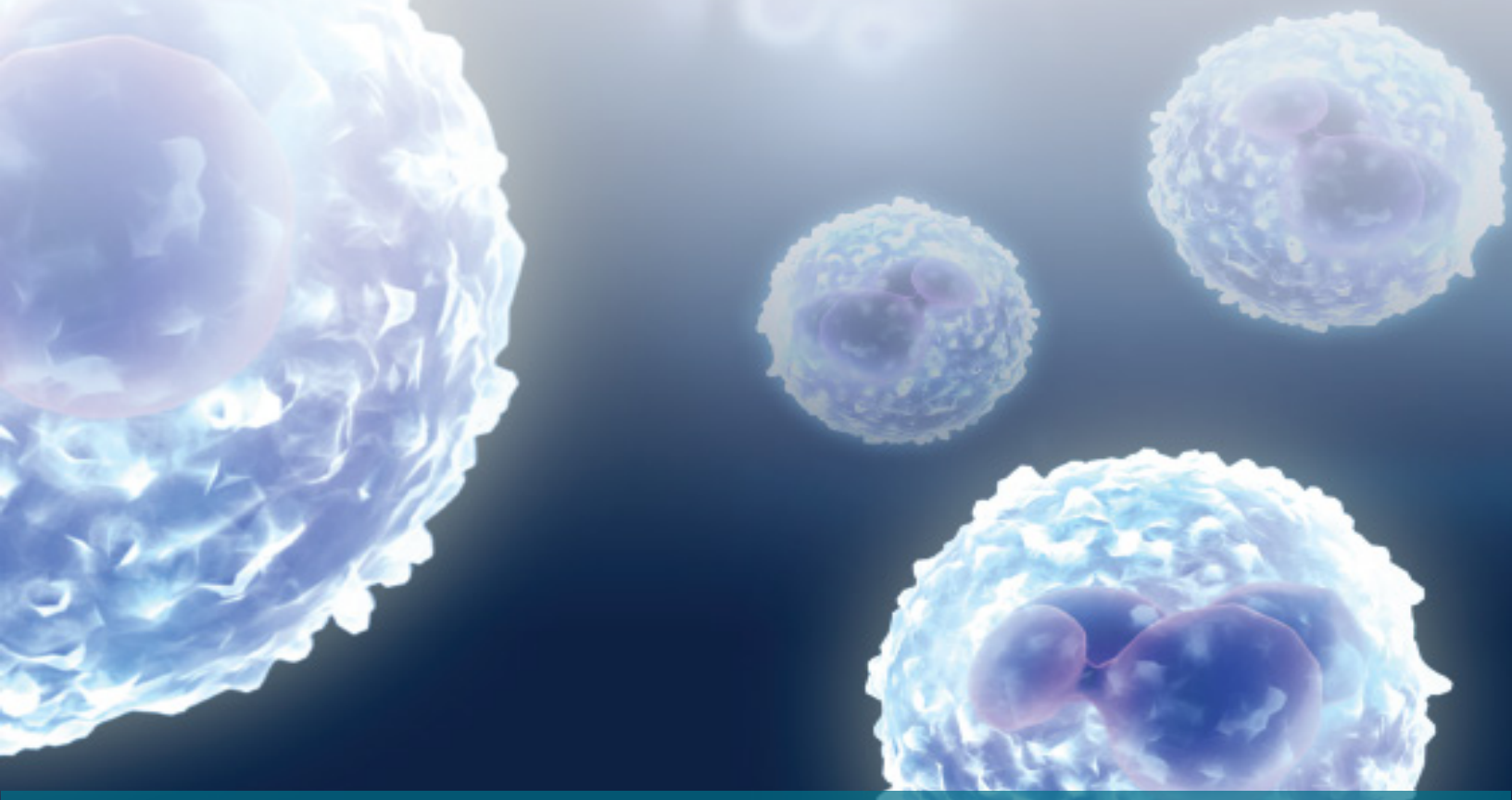
A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis

Robert M. Knobler, MD,[a] Lars E. French,[b] Youn Kim, MD,[c] Emil Bisaccia, MD,[d] Winfried Graninger, MD,[e] Hesam Nahavandi, MD,[a] Frank J. Strobl, MD, PhD,[f] Edward Keystone, MD,[g] Marilyn Mehlmauer, MD,[h] Alain H. Rook, MD,[i] and Irwin Braverman, MD,[j] in the name of the Systemic Sclerosis Study Group*

J Am Acad Dermatol. 2006;54:793-799.

A summary of the findings on the efficacy of extracorporeal photopheresis (ECP) in the treatment of patients with diffuse systemic sclerosis (SSc).‡



From the Department of Dermatology, Medical University of Vienna[a]; Department of Dermatology, Geneva University Hospital[b]; Department of Dermatology, Stanford University School of Medicine[c]; Morristown Memorial Hospital[d]; the Department of Rheumatology, Medical University of Graz[e]; Therakos, Inc, Exton[f]; the Department of Rheumatology, University of Toronto[g]; Huntington Memorial Hospital, Pasadena[h]; the Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia,[i] and the Department of Dermatology, Yale University School of Medicine, New Haven.[j]

*Photopheresis Systemic Sclerosis Study Group members: Ann G. Martin, MD, Washington University School of Medicine, St Louis, Mo; Neil P. Smith, MD, St Thomas Hospital, London, UK (deceased); George P. Stricklin, MD, PhD, Tennessee Valley Healthcare System (Murfreesboro) and Vanderbilt University (Nashville); Bruce U. Wintroub, MD, University of California-San Francisco; Brian Jegasothy, MD, University of Pittsburgh, Pennsylvania (deceased); and David Fivenson, MD, Henry Ford Hospital, Detroit, Mich.

Funding sources: Therakos, Inc.

Disclosure: Drs. Knobler and Bisaccia were paid consultants for Therakos at the time of the study; Dr. Strobl was an employee of Therakos, Inc at the time of the study.

‡The specific instrument system used for this study, the Therakos UVAR XTS photopheresis system, has been replaced by the Therakos CELLEX photopheresis system, and is no longer manufactured or supported.

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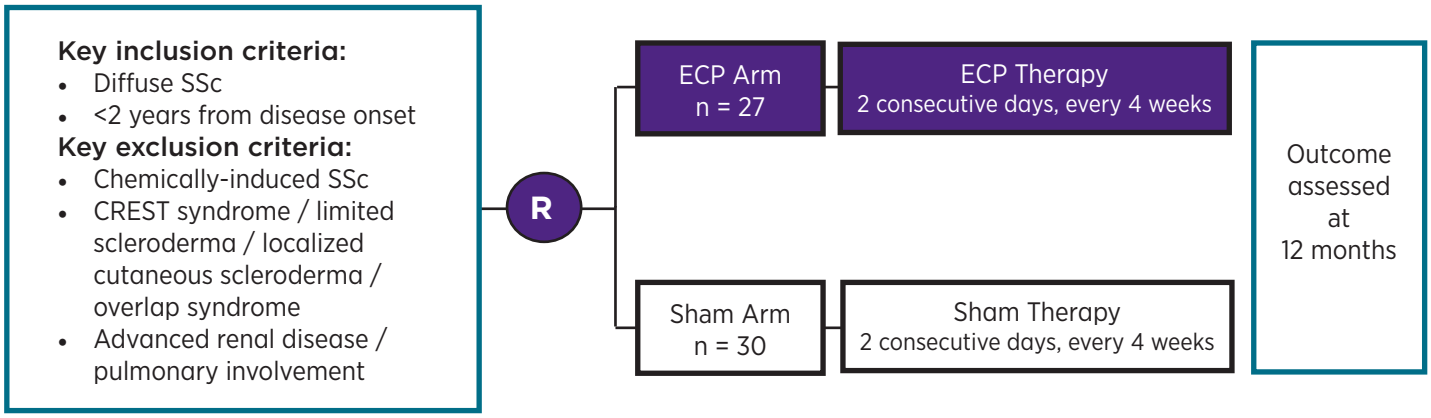
Early-onset scleroderma intervention with THERAKOS™ ECP treatment resulted in significant skin and joint improvement

Background:

The therapeutic options in SSc are limited and are symptom-focused due to challenges in the assessment of therapeutic response with low disease prevalence, and variable prognosis between patients. To investigate the efficacy of ECP in early aggressive scleroderma, a 12-month randomized, double-blind, placebo-controlled trial was performed in patients with diffuse SSc.

Methods:

- 16 investigational sites (Canada, EU, US)
- 57 patients received Therakos™ ECP (n=27) via the UVAR XTS™ or sham‡ ECP (n=30)
- Collagen production-reducing pharmacologic agents, including corticosteroids, colchicine, griseofulvin and D-Pen were not permitted



Outcome Measures:

Assessed monthly for 12 months:

- **Primary**: Decrease in skin involvement evaluated by skin score in 22 regions with the modified scleroderma skin scoring method recommended by Kahaleh et al. (Clin Exp Rheumatol 1986;4:367-9)
- **Secondary**: Change in joint involvement as measured with a goniometer

Limitations:

- Small sample size
- Lack of statistical power to reveal significant differences in skin and joint manifestations between treatment arms
- Only patients with recent onset were included, however time from disease onset may not be a valuable criterion for selecting patients most likely to have progressive disease

Abbreviations: SSc: Systemic Sclerosis, ECP: extracorporeal photopheresis, EU: European Union, US: United States

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BASELINE CHARACTERISTICS

Clinical and demographic characteristics of the patient population studied

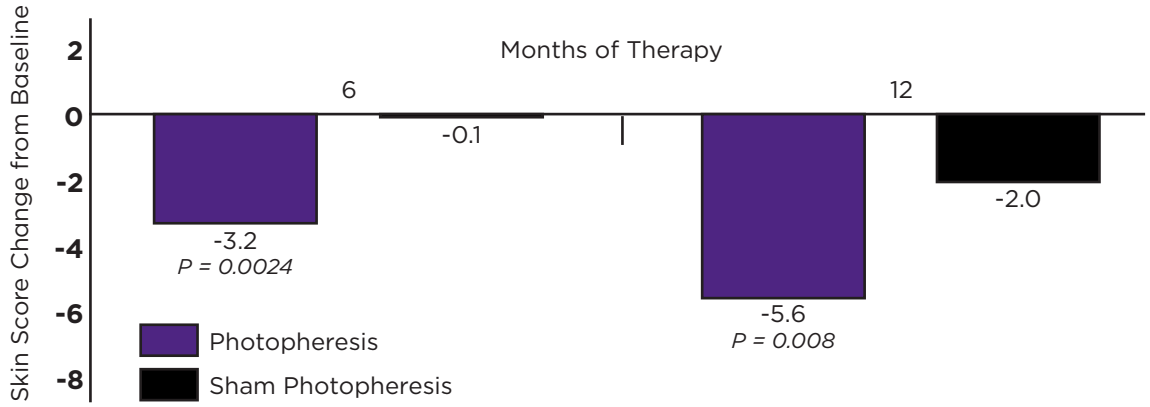
Characteristic	ECP	Placebo
No. of patients	27	30
Age (y) at first treatment Mean Median Range	 39.9 ± 10.7 39.3 21.2 - 63.4	 44.5 ± 11.7 43.9 20.7 - 66.0
Sex (male/female)	4/23	9/21
Disease duration* (y) Mean ± SD Median Range	 1.0 ± 0.5 0.8 0.5 - 2.0	 1.2 ± 0.4 1.1 0.3 - 1.9
Baseline skin severity score (mean ± SD)	34.7 ± 10.8	34.9 ± 10.4

ECP, Extracorporeal photopheresis; SD, standard deviation.
*Calculated from time of diagnosis to time of first treatment.

TRIAL RESULTS

PRIMARY OUTCOME: SKIN IMPROVEMENT IN 22 REGIONS

Therakos™ Photopheresis patients experienced statistically significant skin improvement from baseline at 6 and 12 months



*Comparison of skin scores between the two study arms did not achieve statistical significance because of the small sample size of the study arms.

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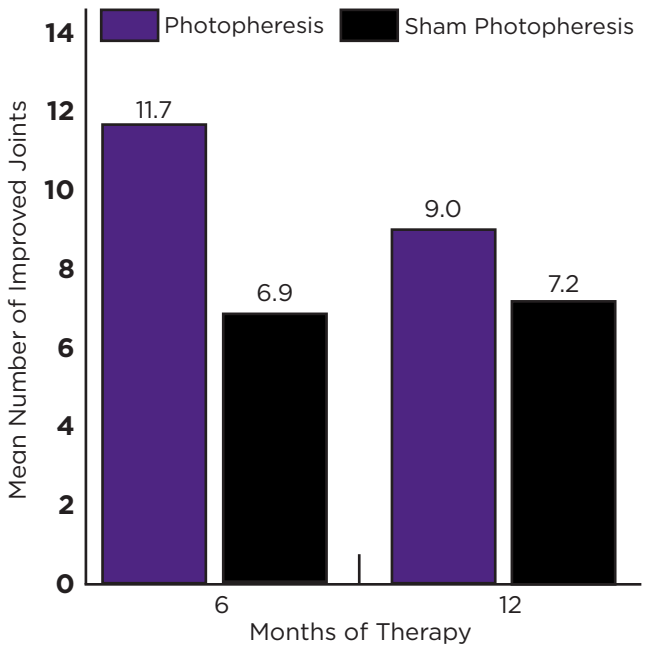
TRIAL RESULTS

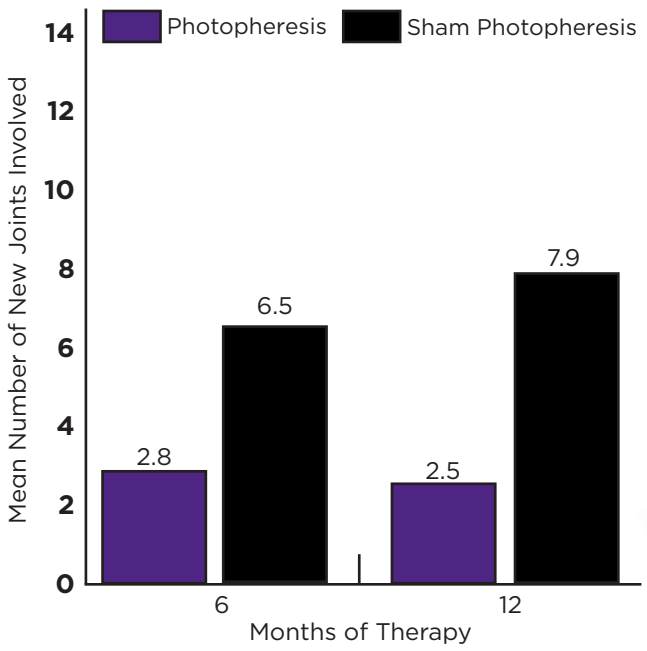
SECONDARY OUTCOME: JOINT INVOLVEMENT

Therakos™ Photopheresis patients experienced improvement in a significantly greater number of joints and had fewer new joints become involved after 6 months (P = 0.002) and 12 months (P = 0.001) of treatment versus baseline

Intra-patient improvement in involved joints from baseline at 6 and 12 months for active and sham ECP arms



Intra-patient new joint involvement from baseline at 6 and 12 months for active and sham ECP arms



"Although this study clearly strengthens the existing evidence that photopheresis can improve both skin and joint involvement in patients with scleroderma, it unfortunately did not have the power to reveal a significant difference in skin involvement between the active and sham photopheresis arms.

Indeed, most likely because of the strict study entry criteria, only 64 patients were enrolled after screening 1000 patients within 3.5 years in 16 centers. On data analysis, it appeared that inclusion of at least another 54 patients would have been needed to detect the presence of any statistically significant difference."

*Please consult additional safety information and list of most common adverse events on page 6 of this reprint carrier.

TRIAL RESULTS

SAFETY & TOLERABILITY

Therakos™ Photopheresis is a well tolerated treatment modality.

No serious adverse events and no significant difference in overall adverse events between study arms were reported.

Study Withdrawals and Adverse Events	Active ECP	Sham ECP
Number of Total Patients Withdrawn	8	12
Consent Withdrawal		
Lost to Follow Up	0	2
Difficulty Traveling	1	1
Unknown Reasons	2	2
Protocol Violation	1	1
Insufficient/Unsatisfactory Therapeutic Effect	3	3
Adverse Experiences (Scleroderma Progression, Renal Crisis and Forgetfulness)	0	2
Neutropenia	1	0
Death	0	1

Conclusions:

Therakos™ Photopheresis treatment resulted in significant skin and joint improvement when compared with baseline levels in patients with early-onset scleroderma.

In general, Therakos™ Photopheresis was well tolerated with no serious side effects reported, and no significant difference in overall side effects between the two study arms.*

Please review the European Dermatology Forum (EDF) 2020 and American Society for Apheresis (ASFA) 2016 guidelines for recommendations on the use of ECP in systemic sclerosis.[1,2]

*Please consult additional safety information and list of most common adverse events on page 6 of this reprint carrier.

1. Knobler R, et al. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16889. 2. Schwartz J, et al. J Clinical Apheresis. 2016;31(3).

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Important Safety Information for THERAKOS™ Photopheresis Procedure

INDICATION:

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) and systemic sclerosis (SSc).

CONTRAINDICATIONS:

Certain underlying medical conditions contraindicate THERAKOS Photopheresis, including:

- Patients who cannot tolerate extracorporeal volume loss during the leukocyte enrichment phase
- Patients exhibiting idiosyncratic or hypersensitivity reactions to 8-methoxypsoralen/psoralen compounds
- 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.

- MR-Unsafe: Do not expose the device to a magnetic resonance (MR) environment. The device may present a risk of projective injury, and thermal injury and burns may occur. The device may generate artifacts in the MR image, or may not function properly.
- Thromboembolic Events: Thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in the treatment of Graft versus Host Disease (GvHD), an indication not approved in Canada. Special attention to adequate anticoagulation is advised when treating patients with 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.

Important Safety Information for Methoxsalen Sterile Solution Used in Conjunction with THERAKOS™ CELLEX Photopheresis System

CONTRAINDICATIONS:

Methoxsalen Sterile Solution is contraindicated in:

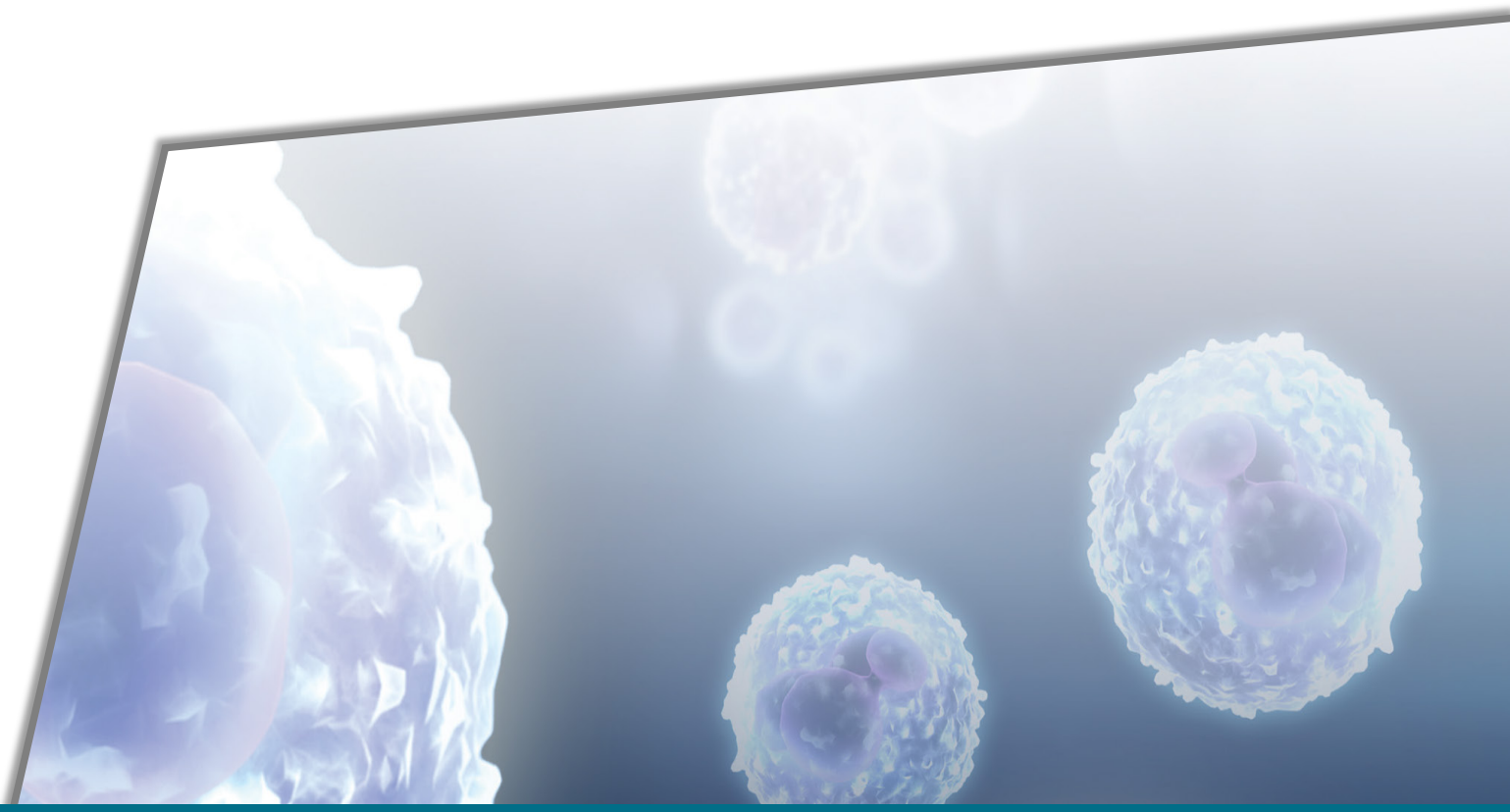
- Patients exhibiting idiosyncratic reactions to psoralen compounds
- Patients with aphakia
- Patients possessing a specific history of a light-sensitive disease state

SERIOUS WARNINGS & PRECAUTIONS:

- Concomitant Therapy: Exercise care in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents.
- Carcinogenicity: Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. Patients exhibiting multiple basal cell carcinomas or having a history of basal cell carcinoma should be diligently observed and treated.
- Teratogenicity: Methoxsalen may cause fetal harm when given to a pregnant woman. Women undergoing photopheresis should be advised to avoid becoming pregnant
- Cataractogenicity: Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after methoxsalen treatment, any time they are exposed to direct or indirect sunlight and whether they are outdoors or exposed through a window.
- Safety in children has not been established.

FOR MORE INFORMATION:

Please consult the full product monograph for methoxsalen sterile solution (if used in conjunction with the THERAKOS™ CELLEX™ Photopheresis System) and the Operator's Manual for the CELLEX system at https://www.mallinckrodt.ca/products/therakos/, or by calling us at 1-877-566-9466.



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