

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-969

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

NDA # 20-969

Submission Date: February 21, 1998

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Sponsor: Therakos, Inc.

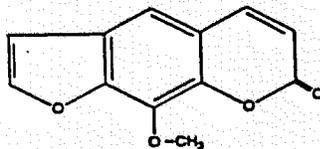
GENERAL DRUG INFORMATION

Drug name: Uvadex® Sterile Solution

Generic name: Methoxalen

Chemical Name: 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one

Chemical Structure:



Chemical formula: $C_{12}H_8O_4$

Molecular weight: 216.18

Pharmacological Category: psoralens or furocoumarins

Proposed Indication

“UVADEX (methoxalen) Sterile Solution is indicated for use with The UVAR Photophoresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in patients who have been unresponsive to other forms of treatment.”

The oral formulation of methoxalen (Oxsoresalen-Ultra Capsules) with long wave UVA radiation is currently approved for three indications: (1) symptomatic control of recalcitrant, disabling psoriasis not adequately responding to other forms of therapy, (2) for repigmentation of idiopathic vitiligo; and (3) for the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma in persons who have not been responsive to other forms of treatment.

The results of the studies submitted will attempt to demonstrate that the proposed use of Uvadex is as effective as the currently approved oral formulation for CTCL with less systemic exposure to the drug.

Pharmacokinetics

Following oral administration, the drug reaches its maximum bioavailability 1-3 hours after administration and may last up to 8 hours. Interpatient variability in C_{max} following oral administration may be as high as 18-fold.¹ This is caused by variable absorption from the gastrointestinal tract, possible interactions with lipid fractions of food, and variable first-pass hepatic elimination.² This variability is avoided with the UVAR system by extracorporeal mixing of the patient's blood and the extracorporeal UVA exposure of the leukocyte concentrated buffy coat followed by reinfusion of the methoxalen treated UVA irradiated cells. Since the total body exposure to methoxalen is substantially lower (approximately 200 times lower) than with oral administration, extracorporeal administration of methoxalen has the pharmacokinetic advantage of having a lower C_{max} and less interpatient variability in serum levels resulting in a reduction in clinical events such as nausea, vomiting, diarrhea, photosensitivity, edema and dizziness.

Pharmacodynamics and Metabolism

The effectiveness of photopheresis for CTCL depends upon achieving a minimum effective serum concentration of at least 50 ng/ml following oral administration of methoxalen.³

CLINICAL BACKGROUND

Reviewer comment: These notations "Reviewer comment" represent the FDA reviewer commentary and evaluation of the study. These are found throughout this NDA review to point out differences in the interpretation of study results, discrepancies in the data, or to emphasize certain aspects of the study that maybe relevant to the marketing approval and/or the approved labeling.

¹ Janses CT, et al. Inter- and intraindividual variation in serum methoxalen levels during repeated oral exposure. *Current Therapeutic Res* 1983; 33(2): 258-264.

² Brickl R, et al. Clinical pharmacology of oral psoralen drugs. *Photodermatology* 1984; 1: 174-186.

³ Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. *New England J Med* 1987; 316: 297-303.

Clinical Presentation

Cutaneous T-cell Lymphoma is a relatively rare neoplasm with an overall incidence of approximately 4 per 1,000,000 according to SEER data. The incidence of CTCL rises with age such that the majority of patients are between 40 and 60. The disease is 2.2 times more common in males than in females, somewhat higher in African Americans than in whites.⁴

Reviewer's comment: Large randomized studies would be difficult to conduct in this rare disease. Small phase 2 studies required participation of multiple centers to accrue the required number of patients.

There are four distinct phases:

- (1) Premycotic phase with an asymptomatic, scaling, erythematous macular eruption often in the sun-shielded areas which lasts for months to years during which the diagnosis may be suspected but cannot be confirmed by standard clinical or histopathologic means.
- (2) Patch phase with thin, barely palpable, erythematous and eczematous lesions whose histopathologic features are at least "consistent with" the diagnosis of CTCL
- (3) Plaque phase with more readily palpable lesions.
- (4) Tumor phase where the neoplastic infiltrate extends below the upper dermis. At this point, the T-cells are highly malignant and lose their affinity for the skin.

Depending on the site and degree of tumor involvement, the first three phases have also been called the epidermatropic stage which manifests itself in the skin and may last between a few years and several decades. The most common sites for lesions to occur are the trunk, thighs and upper arms. At this stage, itching is often the most prominent feature. The tumor phase is also regarded as the nonepidermatropic stage characterized by visceral involvement that may affect the blood, internal organs, lymph nodes and bone marrow. The most important clinical prognostic variables are considered in the staging classification of CTCL. These include the type of lesions and the percent of the total skin surface involved, nodal involvement, dissemination to visceral sites, and the presence of CTCL cells in the circulation.⁵

The diagnosis of CTCL may be challenging, especially in the earlier stages. Skin biopsies at multiple sites may be necessary to define the stage of disease since lesion pathology varies among and within patients. Likewise, typical histopathologic patterns of T-cell lymphoma may be significantly altered by past treatments and concurrent use of medications such as topical steroids.

⁴ Wilson LD. Surveillance, Epidemiology, and End Results (SEER) Program, NCI, October 1995

⁵ Bunn PA, Lamberg SI. Report of the committee on staging and classification of cutaneous T-cell lymphomas. Cancer Treat Rep 1979;63:725.

Therapy

Cutaneous T-cell lymphoma is primarily a disease of the skin lymphocytes. Hence, T1 and T2 stage disease that is localized to the skin has an excellent chance of cure with therapies directed to the skin alone. Therapy can be carried out using DNA alkylating agents such as topical mechlorethamine or BCNU or carmustine. Maintenance topical therapy can also be employed to delay relapse of cutaneous lesions in patients who have achieved a complete response to total skin electron beam therapy (TSEBT) or to treat minimal plaque or patch recurrences after such therapy.⁶ Psoralen Ultraviolet Light Therapy (PUVA) is therapy that is also suitable in this setting. On the other hand, systemically disseminated disease that affect lymph nodes and visceral sites are rarely cured.

Cutaneous photochemotherapy with orally administered psoralen and UVA irradiation of the skin kills cutaneous lymphocytes and interferes with the antigen presentation and cytokine production in the skin. PUVA therapy is able to induce complete remissions in patients with CTCL in the patch or plaque stage. PUVA therapy alone is unlikely to produce a CR for patients with thicker plaques but may be used to maintain the CR's induced by other skin directed therapies. The adjuvant use of PUVA after TSEBT has been shown to increase the relapse-free interval in patients with T1 and T2 disease.⁷ Retrospective analysis of a small number of patients treated with extracorporeal photochemotherapy administered during or after TSEBT appears to improve survival for patients with T3 or T4 disease who have achieved a CR to TSEBT.⁸

Currently Approved PUVA Therapy

Methoxalen (8-methoxypsoralen, 8-MOP) is a member of a group of compounds known as psoralens or furocoumarins. It is a naturally occurring compound that is present in many plants such as citrus, parsley, celery and figs.⁹ The Center of Devices and Radiological Health (CDRH) approved the PMA for the UVAR Photopheresis System on April 8, 1987. The system was indicated for the use with ultraviolet A irradiation, in the presence of the photoactive drug methoxalen, in the extracorporeally circulating leukocyte-enriched blood in

⁶ Prince NM, et al. The treatment of mycosis fungoides: adjuvant topical mechlorethamine after electron beam therapy. *Cancer*, 1977; 40:2851

⁷ Wilson, LD et al. Impact of prognostic factors, adjuvant therapy and retreatment of CTCL patients with TSEBT. (Abs.) Proc 78th Ann Meeting Am Radium Soc, Paris, France. April 29-May 3, 1995

⁸ Wilson LD, et al., Systemic chemotherapy and extracorporeal chemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy. *Int's J Rad Oncol Biol Phys* 1995; 32:987

⁹ Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 200BC to 1992 AD. *J Photochem Photobiol B* 1992; 14(1-2): 3-22.

the palliative treatment of the skin manifestations of CTCL in patients who have not been responsive to other therapy.

Currently approved PUVA therapy requires oral ingestion of 0.6 mg/kg of 8-methoxypsoralen one to two hours prior to the exposure of the skin surface to UVA light (320 to 400nm). To induce remission, treatments should be given three times per week. After most of the lesions have cleared, the frequency of PUVA can be decreased to twice weekly until the patient has achieved a CR.¹⁰ Such a schedule of multiple treatments per week must be maintained for a minimum of three months and a maximum of six months. If a CR has not been established at this time, several strategies can be employed to supplement or enhance the efficacy of PUVA. Such modalities employ local treatment of recalcitrant lesions with spot x-ray or electron beam therapy or systemic treatment with interferons, retinoids, or oral methotrexate.¹¹

Reviewer's comment:

The quality of data on pretreatment staging of patients is crucial in the analysis of efficacy of this treatment modality. It would be important to identify patients with earlier stage disease in contrast to those with late plaque stage and systemic disease since the overall prognosis differs widely. (See result of analysis in section--)

Once a CR is achieved, PUVA is administered once weekly for maintenance therapy for one year. If the remission is sustained, the interval between treatments can be extended to two weeks for an additional year. If there is still no evidence of relapse, the interval between treatments can be extended to three weeks for two years. After five years of maintenance therapy, consideration can be given to cessation of therapy or to extending the treatment intervals to four to six weeks. Patients are not considered "cured" until they have remained disease-free for at least five years after completing therapy.

Basic Principles of Extracorporeal Photochemotherapy (ECP)

Given the intrinsic immunologic nature of cells responsible for CTCL, it is reasonable to infer that agents which modulate T-cell function or other aspects of host immune response should be applied to the therapy of CTCL. ECP involves systemic pretreatment with oral, or parenteral psoralens, removal of a portion of the patient's blood, pheresis of WBC's away from RBCs and exposure of the pheresed WBCs to UVA in an effort to photoactivate intercalated, DNA-bound psoralen to produce psoralen mono-adducts and di-adducts in DNA. The irradiated DNA are then reinfused back to the patient. Such therapy is directly

¹⁰ Honigsmann H, et al. Photochemotherapy for cutaneous T-cell Lymphoma. J AM Acad Dermatol 1984;10:238

¹¹ Thomsen K, Retinoids plus PUVA (rePUVA) and PUVA in MF, plaque stage. A Report from the Scandinavian MF Group. Acta Derm Venereol 1989;69:536.

toxic to the lymphocytes exposed, while the reinfusion of the killed, irradiated CTCL cells appear to selectively stimulate host immune responses against neoplastic T-cells.

Brief Description of the Device and Operation

The Extracorporeal Photopheresis System consists of the (1) UVAR Photopheresis Instrument, (2) the UVAR Tubing Set and the (3) UVAR Cassette.

The **UVAR Photopheresis Instrument** is used during the two phases of the photopheresis treatment: collection and irradiation. It incorporates a reversible blood pump, an anticoagulant pump, a centrifuge for separating the blood fractions during the collection phase, and an ultraviolet irradiation chamber into which the UVAR Cassette is inserted for the irradiation phase.

The **UVAR Cassette** is a six-chambered sterile fluid pathway used for exposing leukocyte-enriched blood to UVA light. Each chamber comprises an outer polycarbonate sheath opaque to UVA light and an inner UVA-transparent acrylic tube surrounding a fluorescent UVA lamp that delivers 201 joules/ml for a typical exposure.

The **UVAR Tubing Set** consists of five packages of lines. The Collection Set, Heparin/Priming Line and Collection Bags are used for the collection phase of the photopheresis treatment. The Recirculation Set is used during the irradiation phase, and the Reinfusion set is used to return the irradiated leukocyte-enriched blood at the end of the photopheresis treatment.

Regulatory History

April 1983	Pre-IND meetings with CDRH and CDB (Center for Drugs and Biologics) for photopheresis after oral ingestion of methoxalen
December 1983	IND submitted for a Phase III study in CTCL
January 1986	PMA submitted to CDRH
July 1986	PMA approval recommended by the Devices and the Gastroenterology-Urology advisory panels. As a condition of the PMA approval, the sponsor agreed to follow the 37 patients enrolled (data submitted in study CTCL 1) and enroll an additional 50 patients (data submitted in study CTCL 2) for a period of five years after approval.
January 1987	A survival analysis and a status update of the 37 evaluable patients were submitted to CDRH and CDER
April 1987	PMA Approved
March 1988	Labeling approval for 8-MOP used with UVAR Photopheresis system granted
February 21, 1998	sNDA for Uvadex/UVAR Photopheresis System submitted to the Division of Oncology

Current Clinical Investigations of UVAR Photopheresis

Table 2. Clinical Investigations of UVAR Photopheresis

Study	IND	Number of Patients	Number of Treatments
AIDS-Related Complex		1	1
CTCL		51	1030
Systemic Sclerosis		30	530
Cardiac Transplant		34	670
Open Label Transplant		29	200
Hepatitis-C		15	175

(from NDA 20,969, vol .1.25, p22)

CLINICAL PROTOCOLS

Reviewer's Comment:

The sponsor submitted data on three phase 2 trials. CTCL 1 and 2 are clinical studies that used the approved oral formulation, while CTCL 3 used the extracorporeal route of administration for which the sponsor is seeking approval. Data from CTCL 1 is a resubmission of data from the original NDA application for oral 8-MOP. Likewise, data on CTCL 2 has been submitted and reviewed by the Agency (CDRH) on July 1992 in compliance with the conditions for approval set forth for oral 8-MOP when it was originally granted.

The final versions of the protocols are the bases for the protocol summaries below. The clinical protocols are discussed concurrently to facilitate comparison and avoid repetition. The main objectives of the FDA review will be as follows: (1) to assess the sponsor's claim that the extracorporeal route of administration offers direct and indirect evidence of at least equivalent efficacy with advantages in safety and pharmacokinetics compared to oral 8-MOP; and (2) to evaluate additional evidence that Uvadex provides both skin responses and meaningful clinical benefits to the patients undergoing treatment.

Study Titles

CTCL 1: Clinical Investigation of the Extracorporeal Photopheresis System

CTCL 2: Clinical Investigation of the UVAR Photopheresis System

CTCL 3: UVADEX® (Liquid 8-MOP®) in Conjunction with the UVAR® Photopheresis System as a Palliative Treatment of the Skin Manifestations of CTCL

Study Dates

CTCL 1: March 1984 to November 1985 (original cut-off date)
May 1992 (administrative cut-off date)

CTCL 2: May 1987 to May 1992

CTCL 3: April 1993 – July 1996

Objectives

CTCL 1

1. To establish the safety of the *in vivo* performance of UVAR Extracorporeal Photophoresis System.

Laboratory Efficacy Endpoints:

- (1) Reduction in the number of viable lymphocytes after seven days, *in vitro*.
 - (2) Inhibition of lymphocyte reproduction after three days, *in vitro*.
2. To verify oral administration of methoxalen followed by photopheresis as efficacious treatment for CTCL.

Clinical Efficacy Endpoint:

- (1) Reduction in overall skin lesion score. A skin response is defined as a 25% reduction in the baseline overall skin lesion score that is maintained for at least four consecutive weeks.

CTCL 2

To establish the safety of the UVAR Photopheresis System and to verify photopheresis as an efficacious treatment for CTCL.

CTCL 3

To demonstrate that the Uvadex formulation of methoxalen administered directly to target cells can have a clinical effect on the skin manifestations of CTCL.

Study Design/ Methodology

CTCL 1 is divided into three phases:

Phase 1: Determination of the oral dose of methoxalen that result in a blood level ≥ 50 ng/mL. The initial dose of 8-MOP is per recommendation in the package insert and adjusted accordingly until the serum 8-MOP concentration reaches a minimum of 50 ng/ml.

Cell viability testing based on trypan blue exclusion on cells obtained from the patient before treatment and from the photoactivation bag after photoactivation. This will also before a patient is released from study.

PHA Stimulation Assay (Cell Proliferation Assay) using ^3H thymidine incorporation to detect DNA synthesis after photoactivation.

Phase 2: Oral dose of methoxalen given prior to UVA exposure of blood. Treatment frequency could vary from 2 daily treatments every 5 weeks to 3 treatments every week as determined by the changes in the patient's skin response or escalated when patients enter into the leukemic phase of the disease.

The rate at which the patient proceeds through the Treatment Schedule outlined below is determined by the patient's skin response as follows:

Step 1: 5-week cycles. Patients receive 2 photopheresis exposures for two consecutive days. Maximum of four cycles (20 weeks).

Elective Step: 2-week cycles as above. Used for patients who do not maintain a response between treatments in Step 1, for those who need to be advanced from step 1 or for those patients who achieve a successful treatment on Steps 2 and 3.

Step 2: weekly cycles as above.

Step 3: weekly cycles, 3 exposures for 3 consecutive days. Maximum of 3 cycles.

Table 3. Treatment Schedule, CTCL 1

Step	Number of Treatments	Number of Days	Frequency of Cycles	Maximum # of Cycles
1	2	2	Q 5 weeks	4
Elective	2	2	Bi-weekly	4
2	2	2	Weekly	4
3	3	3	Weekly	3

Phase 3: A 15-week maintenance schedule of two treatments every five weeks prescribed only for patients who achieve a successful skin response. At the end of Phase 3, the patient was discharged from protocol and started on any therapy deemed necessary. Safety data was collected if photopheresis was continued.

- If the overall skin lesion score increases to 125% of the baseline score during treatment steps 1 and 2, proceed to the next treatment step. If the skin lesion score increases to 125% during Step 3 or to 150% at any time during treatment, the patient is taken off study.
- The first day of treatment in Phase 3 will begin on the day the patient is scheduled to receive the next cycle of treatment from the previous step.
- For patients who develop leukemia: If the WBC count is $\geq 15,000$ with $\geq 50\%$ abnormal cells, advance to the next step regardless of skin lesion score. If the WBC count increases by 100% at 3 separate samplings during a 3-week period, the patient is taken off study. Should abnormal cells decrease by 40%, the patient may be put back into the treatment step in which they were originally treated.

Reviewer's comment: The protocol allowed titration of treatment despite evidence of disease progression. This may be appropriate in clinical practice but the analysis of a study.

CTCL 2

Thirteen study centers participated in the accrual of patients with CTCL into the study. There were no prospectively defined eligibility and exclusion criteria. The protocol defined the treatment administration was similar to CTCL 1. Patients were admitted to the hospital 24 hours before the administration of 8-MOP. The recommended dose was administered one and a half hours prior to starting the collection of leukocytes. The leukocyte enriched blood was recirculated in the UVAR Photopheresis System for 1.5 hours. Precautions for photopheresis therapy were maintained according to the labeling of oral methoxalen

Treatment Schema for CTCL 1 and CTCL 2:

Minus 24 hours:	Admission to hospital
Minus 4 hours:	Fasting to last until one and a half hours after taking methoxalen
Minus 1.5 hours:	Take 0.6 mg/kg 8-MOP orally
0 hour:	Collection of 240 mL leukocytes
0 to 4.5 hour:	Recirculation of leukocyte enriched blood at 100 mL/min in the UVAR Photopheresis System for 4.5 hours
4.5 to 5 hour:	Reinfusion of UVA-light activated blood
5 to 29 hour:	Protection of patients from any UVA light for 24 hours after treatment. Use of protective eyewear and sunscreen recommended.

CTCL 3

This is a single arm, multicenter study. The following steps are followed during treatment :

Collection of leukocyte enriched blood : 300 ml of plasma and 240 ml buffy coat are separated and saved in six cycles of blood collection.

Photoactivation: Uvadex, 200 mcg is injected into the first buffy coat bag. The plasma and buffy coat are then mixed with 200 ml of heparinized saline and circulated through the photoactivation chamber. Photoactivation is applied for an additional 90 minutes after the sixth cycle of buffy coat is collected.

Reinfusion : Done by gravity over 30 to 45 minutes.

Frequency of Treatment: two consecutive days every four weeks for a minimum of seven treatment cycles (six months). (Amendment dated November 1993: An additional six months of treatment may be given for a total of one year. During this "follow-up" period, patients continued to receive treatment under the usual or the accelerated schedule.)

If the skin score is increased by the fourth treatment cycle (approximately three months) the frequency of treatment could be increased to two consecutive days every two weeks (accelerated schedule). Patients who attained a 25% improvement in skin scores reverted to the regular schedule. Patients who are retained in the accelerated treatment schedule may receive a maximum of 20 cycles.

Reviewer's comment: Patients who do not respond initially may be given treatment for as long as one year. This may be reasonable for a disease with a relatively long natural history and very few treatment options. However, it is also important to estimate the optimal duration of treatment.

In CTCL 1 and 3, patients who develop skin tumors exceeding 1.5 cm in diameter received one or a combination of the following therapies:

- Superficial radiotherapy
- Surgical excision
- Cryotherapy

Patients with severe pruritus may receive localized topical application of steroid cream twice daily for no more than two weeks. Data from the overall skin lesion score will be gathered but not used to advance the patient in the study nor included in the statistical analysis. The period in question begins during the two weeks the patient is treated with the steroid cream and for one week after the last dose.

Cell viability testing and PHA Stimulation Assay were also done on Visits #1, 4, 7, 10 and 12. Methoxalen plasma levels were determined at every treatment, thirty minutes after the reinfusion of the photoactivated cells.