CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-969

Trade Name: UVADEX Sterile Solution, 20 mcg/mL

Generic Name:(methoxsalen)

Sponsor: Therakos, Inc.

Approval Date: February 25, 1999

Indication: Provides for the use of UVADEX (methaxsalen) Sterile Solution with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment,

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Application Number:NDA 20-969

APPROVAL LETTER

D. Catlerson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-969

FEB 25 1999

THERAKOS, Inc.
437 Creamery Way
Exton, PA 19341

Attention: Peggy Schwartz
Manager, Regulatory Affairs

Dear Ms. Schwartz:

Please refer to your new drug application (NDA) dated February 20, 1998, received February 25, 1998, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for UVADEX® (methoxsalen) Sterile Solution, 20 mcg/mL.

We acknowledge receipt of your submissions dated March 19 and 26; April 16, 17, and 29; May 8 and 11; June 10; August 21; September 10; and November 16, 1998; and January 6, 1999. The user fee goal date for this application is February 25, 1999.

This new drug application provides for the use of UVADEX® (methoxsalen) Sterile Solution with the UVAR® Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-969." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Debra Catterson, Project Manager, at (301) 827-1544.

Sincerely,

/S/ , M.D.

Robert Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

APPROVED

FEB 25 1999

Rx only.

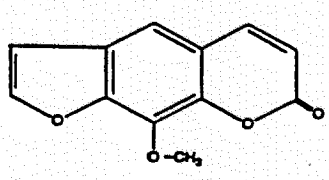
CAUTION: READ THE UVAR® PHOTOPHERESIS SYSTEM OPERATOR'S MANUAL PRIOR TO PRESCRIBING OR DISPENSING THIS MEDICATION.

UVADEX® (Methoxsalen) STERILE SOLUTION, 20 mcg/mL

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 UVAR® Photopheresis System. Please consult the UVAR® Photopheresis System Operator's Manual before using this product.

DESCRIPTION

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the Ammi majus (Umbelliferae) plant. It belongs to a group of compounds known as psoralens or furocoumarins. The chemical name of methoxsalen is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one; it has the following structure:



Each mL of UVADEX® (methoxsalen, 8-methoxypsoralen) Sterile Solution contains methoxsalen 20 mcg, propylene glycol 50 mg, sodium chloride 8 mg, sodium acetate 1.75 mg, ethanol 0.05 mL, glacial acetic acid 0.0012 mL, and Water for Injection q.s. to 1.0 mL.

UVADEX® is used in combination with the UVAR® Photopheresis System to extracorporeally treat leukocyte enriched buffy coat.

CLINICAL PHARMACOLOGY

Mechanism of action: The exact mechanism of action of methoxsalen is not known. The best-known biochemical reaction of methoxsalen is with DNA. Methoxsalen, upon photoactivation, conjugates and forms covalent bonds with DNA which leads to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking of psoralen to both strands of DNA). Reactions with proteins have also been described.

For the palliative treatment of cutaneous T-cell lymphoma, the UVAR® Photopheresis System removes a portion of the patient's blood and separates the red blood cells from the white cell layer (buffy coat) by centrifugation. The red cells are returned to the patient and the UVADEX® Sterile Solution is then injected into the UVAR® system and mixed with the buffy coat. The UVAR® system then irradiates this drug-cell mixture with ultraviolet light (UVA light, 320–400 nm) and returns the treated cells to the patient. See the UVAR® Photopheresis System Operator's Manual for details of this process. Although extracorporeal phototherapy exposes less than 10% of the total body burden of malignant cells to methoxsalen plus light, some patients achieve a complete response. Animal studies suggest that the photopheresis may activate an immune-mediated response against the malignant T-cells.

Use of the UVAR® system after oral administration of methoxsalen was previously approved for the treatment of cutaneous T-cell lymphoma. Interpatient variability in peak plasma concentration after an oral dose of methoxsalen ranges from 6 to 15 fold. UVADEX® is injected directly into the separated buffy coat in the UVAR® system in an attempt to diminish this interpatient variability and to improve the exposure of the cells to the drug.

Methoxsalen is reversibly bound to serum albumin and is also preferentially taken up by epidermal cells. Methoxsalen is rapidly metabolized in humans, with approximately 95% of the drug excreted as metabolites in the urine within 24 hours.

Systemic administration of methoxsalen followed by UVA exposure leads to cell injury. The most obvious manifestation of this injury after skin exposure is delayed erythema, which may not begin for several hours and peaks at 48-72 hours. The inflammation is followed over several days to weeks, by repair which is manifested by increased melanization of the epidermis and thickening of the stratum corneum.

The total dose of methoxsalen used with the UVAR® system in conjunction with UVADEX® is substantially lower (approximately 200 times) than that used with oral administration.

CLINICAL STUDIES

Three single-arm studies were performed to evaluate the effectiveness of photopheresis in the treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL). In the first study (CTCL 1), 39 patients were treated with the oral formulation of methoxsalen in conjunction with the UVAR® Photopheresis System. The second study (CTCL 2) was a 5-year post approval follow-up of 57 CTCL patients that was conducted to evaluate long-term safety. This study also used the oral dosage formulation of methoxsalen. In the third study (CTCL 3), 51 patients were treated with the UVADEX® formulation of methoxsalen in conjunction with the UVAR® Photopheresis System. In study CTCL 3, 86% of the patients were Caucasian, the median age was 62 years, and the average number of prior therapies was 4.3.

In study CTCL 1, prednisone up to 10 mg/day was permitted in addition to topical steroids. In CTCL 2, there was no concomitant medication restriction. In CTCL 3, topical steroids were permitted only for the treatment of fissures on the soles of the feet and the palms of hands. All other steroids, topical or systemic, were prohibited.

In all three studies, patients were initially treated on two consecutive days every four to five weeks. If the patient did not respond after four cycles, treatment was accelerated to two consecutive days

every other week. If the patient did not respond after four cycles at the accelerated schedule, the patient was treated on two consecutive days every week. If the patient still did not respond after four cycles of weekly treatments, the schedule was increased to three consecutive days every week for three cycles. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment. Only two patients responded to treatment after six months. Clinical experience does not extend beyond this treatment frequency and there is no evidence to show that treatment with UVADEX® beyond six months or using a different schedule provided additional benefit.

Overall skin scores were used in the clinical studies of photopheresis to assess the patient's response to treatment. The patient's baseline skin score was used for comparison with subsequent scores. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy. Table 1 indicates the percent of successful responses within six months of beginning therapy for all patients who received at least one course of photopheresis. Only patients with patch plaque, extensive plaque and erythrodermic disease were enrolled in these studies. There are no data available regarding the efficacy of UVADEX® in patients with disease in the tumor phase.

Table 1: Percentage of Successful Responses Within Six Months of Beginning Therapy

Study	Response % Within Six Months
CTCL 3 (UVADEX®)	17/51 (33)
CTCL 2 (oral methoxsalen)	16/57 (28)
CTCL 1 (oral methoxsalen)	21/39 (54)

Although the response rate with UVADEX® in CTCL 3 was similar to that with oral methoxsalen in CTCL 2, the possibility that UVADEX® is inferior in efficacy to oral methoxsalen cannot be

excluded due to the design and size of the clinical trials. The higher response rate with oral methoxsalen in CTCL 1 may be partly due to patients receiving more treatments (mean of 64 in CTCL 1, 31 in CTCL 2, and 20 in CTCL 3), and to the administration of systemic steroids in CTCL 1.

Retrospective analyses of three clinical benefit parameters from the Body Area Severity Scores in CTCL 3 suggested a correlation between skin score response and improvement in edema, scaling and resolution of fissures.

INDICATIONS AND USAGE

UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

CONTRAINDICATIONS

PHOTOSENSITIVITY: UVADEX® (methoxsalen) Sterile Solution is contraindicated in patients exhibiting idiosyncratic reactions to psoralen compounds. Patients possessing a specific history of a light sensitive disease state should not initiate methoxsalen therapy. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum and albinism.

UVADEX® Sterile Solution is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses.

WARNINGS

Concomitant Therapy: Special care should be exercised in treating 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.

Carcinogenicity, Mutagenesis, Impairment of Fertility: Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. In a prospective study of 1380 patients given PUVA therapy for psoriasis, 237 patients developed 1422 cutaneous squamous cell cancers. This observed incidence of cutaneous carcinoma is 17.6 times that expected for the general population. Previous cutaneous exposure to tar and UVB treatment, ionizing radiation or arsenic increased the risk of developing skin carcinomas after PUVA therapy. 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.

Methoxsalen was carcinogenic in male rats that were given the drug by oral gavage five days per week for 103 weeks at doses of 37.5 and 75 mg/kg. The 37.5 mg/kg dose is about 1900 times greater than a single human methoxsalen dose during extracorporeal photopheresis treatment on a body surface area basis. The neoplastic lesions in rats included adenomas and adenocarcinomas of the tubular epithelium of the kidneys, carcinoma or squamous cell carcinoma of the Zymbal gland and alveolar or bronchiolar adenomas. Topical or intraperitoneal methoxsalen is a potent photo-carcinogen in albino mice and hairless mice.

With S9 activation, methoxsalen is mutagenic in the Ames test. In the absence of S9 activation and UV light, methoxsalen is clastogenic *in vitro* (sister chromatid exchange and chromosome aberrations in Chinese hamster ovary cells). Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair.

Pregnancy: Methoxsalen may cause fetal harm when given to a pregnant woman. Doses of 80 to 160 mg/kg/day given during organogenesis caused significant fetal toxicity in rats. The lowest of these doses, 80 mg/kg/day, is over 4000 times greater than a single dose of UVADEX® on a mg/m^2 basis. Fetal toxicity was associated with significant maternal weight loss, anorexia and increased relative liver weight. Signs of fetal toxicity included increased fetal mortality, increased resorptions, late fetal death, fewer fetuses per litter, and decreased fetal weight. Methoxsalen caused an increase in skeletal malformation and variations at doses of 80 mg/kg/day and above. There are no adequate and well-controlled studies of methoxsalen in pregnant women. 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. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General:

ACTINIC DEGENERATION:

After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin.

BASAL CELL CARCINOMAS:

Patients exhibiting multiple basal cell carcinomas or having a history of basal cell carcinomas should be diligently observed and treated.

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 not followed.

THE FORMATION OF CATARACTS:

Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity. The concentration of methoxsalen in the human lens is proportional

to the concentration in serum. Serum methoxsalen concentrations are substantially lower after extracorporeal UVADEX ® treatment than after oral methoxsalen treatment. Nevertheless, if the lens is exposed to UVA light while methoxsalen is present, photoactivation of the drug may cause adducts to bind to biomolecules within the lens. If the lens is shielded from UVA light, the methoxsalen will diffuse out of the lens in about 24 hours.

Patients who use proper eye protection after PUVA therapy (oral methoxsalen) appear to have no increased risk of developing cataracts. The incidence of cataracts in these patients five years after their first treatment is about the same as that in the general population. Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (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.

Information for Patients:

Patients should be told emphatically to wear UVA-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SP 15 or higher) for the twenty-four (24) hour period following treatment with methoxsalen, whether exposed to direct or indirect sunlight in the open or through a window glass.

Drug Interactions:

See Warnings Section.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

See Warnings Section.

Pregnancy:

Pregnancy Category D. See Warnings Section.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methoxsalen is administered to a nursing woman.

Pediatric Use:

Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenicity as described in the Warnings Section as well as the probability of actinic degeneration which is also described in the Warnings Section.

ADVERSE REACTIONS

Side effects of photopheresis (UVADEX® used with the UVAR® Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%). In study CTCL 3 (UVADEX®), six serious cardiovascular adverse experiences were reported in five patients (5/51, 10%). Five of these six events were not related to photopheresis and did not interfere with the scheduled photopheresis treatments. One patient (1/51, 2%) with ischemic heart disease had an arrhythmia after the first day of photopheresis, but this had resolved by the next day. Six infections were also reported in five patients. Two of the six events were Hickman catheter infections in one patient, which did not interrupt the scheduled photopheresis. The other four infections were not related to photopheresis and did not interfere with scheduled treatments.

OVERDOSAGE

There are no known reports of overdosage with extracorporeal administration of methoxsalen. However, in the event of overdosage, the patient should be kept in a darkened room for at least 24 hours.

DRUG DOSAGE AND ADMINISTRATION

Each UVADEX® treatment involves collection of leukocytes, photoactivation, and reinfusion of photoactivated cells. UVADEX® (methoxsalen) Sterile Solution is supplied in 10 mL vials containing 200 mcg of methoxsalen (concentration of 20 mcg/mL). During each photopheresis treatment performed with UVADEX®, 10 mL (200mcg) of UVADEX® is injected directly into the

photoactivation bag during the first buffy coat collection cycle. At the end of six cycles, a total of 740 mL (240 mL of buffy coat, 300 mL of plasma, and 200 mL of normal saline priming fluid) is collected and mixed with the 200 mcg of UVADEX® present in the photoactivation bag. After photoactivation the cells are reinfused. The UVAR® Photopheresis System Operator's Manual should be consulted before using this product.

Frequency/Schedule of Treatment:

Normal Treatment Schedule:

UVADEX® treatment is given on two consecutive days every four weeks for a minimum of seven treatment cycles (six months).

Accelerated Treatment Schedule:

If the assessment of the patient during the fourth treatment cycle (approximately three months) reveals an increased skin score from the baseline score, the frequency of treatment may be increased to two consecutive treatments every two weeks. If a 25% improvement in the skin score is attained after four consecutive weeks, the regular treatment schedule may resume. Patients who are maintained in the accelerated treatment schedule may receive a maximum of 20 cycles. There is no clinical evidence to show that treatment with UVADEX® beyond six months or using a different schedule provides additional benefit. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment and only two patients responded to treatment after six months.

HOW SUPPLIED

UVADEX® (methoxsalen) Sterile Solution 20 mcg/mL in 10 mL vials (NDC xxxx-xxxx-xx), and cartons of 12 vials (NDC xxxx-xxxx-xx). The drug product must be stored between 59°F (15°C) and 86°F (30°C).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling of Parenteral Antineoplastics. JAMA, 1985; 2.53 (11): 1590-1592.

3. National Study Commission on Cytotoxic Exposure- Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from The Mount Sinai Medical Center. CA- A Cancer Journal for Clinicians, 1983;(Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin of Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990;47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), AM J. Health-Syst Pharm, 1996; 53: 1669-1685.

cc:
Archival NDA 20-969
HFD-150/Div. Files
HFD-150/DCatterson
HFD-150/IChico
HFD-150/GWilliams
HFD-150/YHsieh
HFD-150/RWood
HFD-150/WMcGuinn
HFD-150/PAndrews
HFD-150/NLi
HFD-150/GChen
HFD-150/JDuan
HFD-150/ARahman
HFD-150/MMehta
HFD-150/LVaccari
HFD-150/DPease
HFD-150/D.Catterson
HFD-150/D.Catterson
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: DCatterson/February 22, 1999
Initialed by:
HFD-150/DPease/2.23.99
HFD-150/IChico/2.23.99
HFD-150/GWilliams/2.24.99
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APPROVAL (AP)