CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-969

CHEMISTRY REVIEW(S)

Catterson

JAN 28 1999

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150

Review of Chemistry, Manufacturing and Controls

NDA No: 20-969 **Chem. Review No.: 01** **Review Date: January 12, 1999**

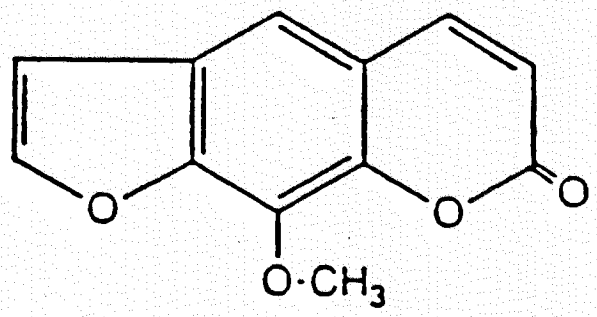
Submission Type	Document Date	CDER Date	Date Received
Original	February 20, 1998	February 25, 1998	March 12, 1998
Amendment (BC)	April 29, 1998	April 30, 1998	June 5, 1998
Amendment (BC)	May 8, 1998	May 11, 1998	June 5, 1998
Amendment (BC)	May 12, 1998	May 12, 1998	June 5, 1998
Amendment (BC)	November 16, 1998	November 17, 1998	December 16, 1998

Name and Address of Applicant: THERAKOS, Inc.
437 Creamery Way
Exton, PA 19341

Drug Product Name

Proprietary:	N/A
Nonproprietary/USAN:	Uvadex® Sterile Solution (methoxsalen, 20 mg/mL)
Chem. Type/Ther. Class:	1S/antineoplastic

Chemical Name, Structural Formula, Molecular Formula, Mol. Weight:



Chemical Name:	9-Methoxy-7H-furo[3,2-g][1]benzopyran-7-one]
Molecular Formula:	$C_{12}H_8O_4$
Molecular Weight:	216.18
Generic Name:	methoxsalen
CAS Registration No.:	298-81-7

Related Documents:

IND	THERAKOS, Inc.; Uvadex

Consults:

EER	Pending	
Methods Validation	Hold	Methods require modifications
Microbiology	Completed	
Statistics	Pending	
EA	Completed	

Remarks and Comments:

The drug product Uvadex®, a photoactive drug, is to be used with the UVAR® Photopheresis System for the irradiation of extracorporeally circulating leukocyte-enriched blood in the pallative treatment of the skin manifestations of cutaneous T-cell lympoma (CICL) in patients who have not been responsive to other forms of treatment. The photopheresis system is currently used (NDA 09048) in conjunction with oral 8-methoxasalen (8-MOP®) for the same indication. It consists of the UVAR Instrument, 4 blood tubing lines, the PHOTOCEPTOR® photoactivation chamber, the PHOTOSETTE® (a light assembly) and a centrifuge bowl.

In the photopheresis process, the patient is connected to the instrument at approximately 2 h after ingestion of a dose of 8-MOP® sufficient to raise the level of 8-methoxasalen in blood to 50 ng/mL or greater. Blood is pumped into the centrifuge bowl, which separates the blood into white blood cells, red blood cells and plasma, by centrifuge. The red blood cells are returned to the patient after each cycle without being exposed to UV light. A portion of the plasma and the white blood cells are collected into the photoactivation chamber and irradiated with the UV light which causes the methoxsalen in the nucleated white blood cells to form covalent bonds in the pyrimidine bases of the DNA, thereby preventing further replication of the cell. After irradiation, the plasma and the white blood cells are returned to the patient. It is believed that when the lethally-injured white blood cells are reinfused into the patient, surface antigens on the abnormal cells cause the host immune system to recognize the clones of the untreated malignant cells. This may result in a true biologic response modification and induction of a favorable immune response to the underlying malignancy.

However, the crystalline oral 8-MOP currently used in the photopheresis has poor bio-availability. The applicant reported that 20% of the patients undergoing photopheresis therapy have 8-methoxasalen drug levels in blood lower than 50 ng/mL. In the current application, Therakos is seeking approval to inject UVADEX sterile solution at a dose of 200 μg directly into the photoactivation bag, where the plasma and the white blood cells are collected, to achieve a concentration of 270 ng/mL of fluid in the bag. The spiked plasma and the white blood cells are pumped into the PHOTOCEPTOR and continuously circulated through the chamber while being photoactivated. After one collection cycle is completed, the red blood cells and excess plasma are returned to the patient while the white blood cells and some plasma continue to circulate through the PHOTOCEPTOR. At the end of the photoactivation cycle, these photoactivated cells are then reinfused into the patient through the return bag.

Methoxsalen, the drug substance, is a naturally-occurring, photoactive substance found in the seed of the Ammi majus (umbelliferae) plant; it belongs to a class compound known as psoralens or furocoumarins. The extraction of crude methoxsalen is described in DMF Purification of the crude material is performed at and tested for release by

Currently, the oral dosage formulation of methoxsalen, 8-MOP® , is approved for use with the UVAR Photopheresis System.

The drug product, UVADEX methoxsalen Sterile Solution (20 μg/mL) will be manufactured and released by The stability testing of the drug product is performed by

Conclusion and recommendation

Adequate CMC data have been submitted to support the identity, strength, quality and purity of the UVADEX sterile solution. Approval is recommended.

/S/ 1-12-99

Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

/S/ 1-28-99

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

cc:
Orig. NDA 20-969
HFD-150/Division File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/DCatterson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-969

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

UVADEX®

(methoxsalen)

Sterile Injection

NDA 20-969

Food And Drug Administration

Center For Drug Evaluation And Research

Division of Oncologic Drug Products (HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-969

UVADEX® (methoxsalen) Sterile Injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process. The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not, individually or cumulatively, have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **UVADEX® (methoxsalen) Sterile Injection, Therakos, Inc.** has prepared an environmental assessment in accordance with 21 CFR Part 25 (attached) which evaluates the potential environmental impacts of use of the product. The application provides for a new dosage form/dosing regimen of methoxsalen for the palliative treatment of cutaneous T-cell lymphoma (CTCL), a low-grade, non-Hodgkin's lymphoma characterized by proliferation of helper T-cells that infiltrate the skin. A solid oral dosage form (capsule) of methoxsalen is currently approved for this use. The amount of UVADEX® needed per treatment is 200 μg as compared to 40 mg for the solid oral dosage form. UVADEX® will be used in hospitals and clinics.

The drug substance is obtained from the seeds (fruits) of both cultivated and wild *Ammi majus* plants. The plant grows wild and cultivated in several parts of Egypt. The rapidly growing plant is dense and more common along the banks of the Nile River in the northern delta region of Egypt. Renewable resources are used. When the plant is ripe with fruits, which develop on the end of long umbels, the fruits are separated from the stalks by lightly tapping the umbels. The harvesting process does not damage or destroy the plant. *Ammi majus* is not listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Methoxaslen is currently approved by FDA for the treatment of CTCL. Approval of this new dosage form/dosing regimen will reduce the amount of biomass needed to supply methoxsalen for the treatment of this life threatening disease.

Disposal in the United States may result from returned or rejected product and user disposal of empty or partly used product and packaging. Returned or rejected product will be sent by Therakos, Inc. to a licensed disposal facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

The Center for Drug Evaluation and Research has concluded that the product can be used without any expected adverse environmental effects.

9/4/98
DATE

/S/
PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

9-8-98
DATE

/S/
CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

c.c. original to NDA 20-969 through DCatterson/HFD-150
HFD-357/EA File NDA #20-969
HFD-357/Docket File
HFD-205/FOI COPY

1. Date

This report was prepared on August 20, 1998.

2. Name of Applicant

Therakos, Inc.

3. Address

437 Creamery Way
Exton, PA 19341

4. Description of Proposed Action

a) Requested Approval

Therakos has filed NDA 20-969 for UVADEX® methoxsalen Sterile Solution 20μg/ml packaged in 10 ml amber vials. This Environmental Assessment is submitted pursuant to 21 CFR Part 25.

b) Need for Action

Therakos, in conjunction with Hoffman-LaRoche, has developed UVADEX methoxsalen Sterile Solution, a liquid formulation of methoxsalen. The drug product is intended to be used in conjunction with Therakos' UVAR® Photopheresis System for the palliative treatment of cutaneous T-cell lymphoma (CTCL), a low-grade, non-Hodgkin's lymphoma characterized by proliferation of helper T-cells that infiltrate the skin. CTCL affects approximately 0.4/100,000 persons. The initial skin lesions are clinically and histologically non-specific, making definitive diagnosis difficult. When the diagnosis is made, usually because of a skin biopsy, the disease is typically confined to the skin an initial therapy is usually directed there. However, as the disease progresses, there is involvement of visceral organs, with or without the detection of circulating atypical lymphocytes with hyperconvoluted nuclei (Sézary cells). The prognosis for patients with advanced disease is poor, with a median survival of approximately 40 months. Therapy for advanced disease is problematic because treatments often result in high morbidity without substantial long-term benefits.

b) Need for Action (Cont'd)

Photoactivation of methoxsalen has been shown to interact with DNA within the malignant T-cell nucleus, leading to breaks in the DNA strands and subsequent apoptotic cell death. Photopheresis using an oral crystalline formulation of methoxsalen has been approved in the U.S. and some European countries as extracorporeal photomedical therapy indicated for the palliative treatment of the skin manifestations of CTCL. However, a major problem associated with oral methoxsalen is that its bioavailability is both variable and unpredictable. Approximately 20% of patients are found to have sub-therapeutic drug levels while others develop blood levels greatly in excess of what is considered necessary for optimal effect upon photoactivation. Such high drug levels increase the likelihood of systemic adverse reactions (mainly nausea and photosensitivity reactions). Because UVADEX methoxsalen Sterile Solution is administered extracorporeally, a much smaller amount of drug is required, and the methoxsalen concentration can be achieved very precisely with virtually no measurable systemic exposure to the drug.

During photopheresis treatment with UVADEX methoxsalen Sterile Solution, the patient's blood is withdrawn and pumped into a centrifuge bowl. White blood cells are separated by centrifugation to create a leukocyte-rich buffy coat (the reddish gray layer observed above packed red blood cells) fraction. The red blood cells and excess plasma are returned to the patient, while the buffy coat fraction is collected into a bag on the side of the photopheresis unit. The collection process is repeated six (6) times. UVADEX methoxsalen Sterile Solution is administered extracorporeally by injecting the solution directly into the photoactivation collection bag. The buffy coat suspension is then circulated through the photoactivation chamber (photoceptor) for 90 minutes while being exposed to ultraviolet-A (UVA) light (1-2 J/cm^2). The photoactivated cells are reinfused into the patient at the end of the photoactivation cycle.

c) Locations of Use

UVADEX methoxsalen Sterile Solution will be administered as part of the UVAR Photopheresis procedure, which is conducted either on an in-patient or out-patient basis in clinics and hospitals under medical supervision.

d) Disposal Sites

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures.

Returned or rejected product will be disposed of by Therakos using licensed solid waste management companies according to local solid waste

management systems, which may include landfills, incineration and recycling. Minimal amounts of unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject of the Proposed Action

a) Nomenclature

a

i. Established Name (USAN)

Methoxsalen

ii. Brand/Proprietary Name/Trade Name

UVADEX® methoxsalen Sterile Solution

iii. Chemical Name(s)

- Chemical Abstracts (CA) Index Name

  9-methoxy-7*H*-furo[3,2-g][1]benzopyran-7-one

- Systematic Chemical Name

  7*H*-furo[3,2-g][1]benzopyran-7-one, 9-methoxy-

b) Chemical Abstracts Service (CAS) Registration Number

298-81-7

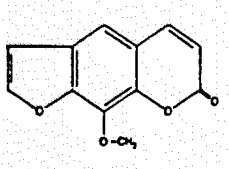
b c) Molecular Formula

$C_{12}H_8O_4$

d) Molecular Weight

216.18

e) Structural (Graphic) Formula



6. Environmental Issues

a) Assessing Toxicity to Environmental Organisms

1) Approval Will Not Increase the Use of the Active Moiety (Methoxsalen)

UVADEX methoxsalen Sterile Solution is intended to be used in conjunction with Therkos' UVAR Photopheresis System for the palliative treatment of the skin manifestations of cutaneous t-cell- lymphoma (CTCL), a low-grade, non-Hodgkin's lymphoma. The proposed indication is identical to that for the approved oral (capsule) formulation of methoxsalen. However, because UVDEX methoxsalen Sterile Solution is administered extracorporally, a much smaller amount of methoxsalen is required to achieve the desired effect with virtually no systemic exposure to the drug. Consequently, the dosing regimen for methoxsalen capsules is 40 mg (0.6 mg/kg of body weight) compared to 200 µg for UVADEX methoxsalen Sterile Solution for each treatment; treatment frequency is typically two treatments per month. Therefore, approval of this application will result in lower doses of methoxsalen than previously approved for the same indication.

2) The Estimated Concentration of Methoxsalen at the Point of Entry into the Aquatic System is below 1 Part per Billion

The anticipated maximum production level for methoxsalen drug substance based on the five-year (1998-2002) production level is one 57 g lot per year. Based on this production level the expected introduction concentration (EIC) of methoxsalen into the aquatic environment is:

Estimated Introduction Concentration (EIC) = A*B*C*D, where

A=kg/yr production (as methoxsalen)
B=$1/1.115*10^{11}$ liters/day entering publicly-owned treatment works
C=1 yr/365 days
D=10^9 µg/kg (conversion factor)

EIC = $(114*10^{-3}$ kg/yr)*$(1/1.115*10^{11}$ liters/day)*(1 yr/365 days)*$(10^9$ µg/kg)
= $1.40*10^{-6}$ µg/liter
= $1.40*10^{-6}$ ppb

6. Environmental Issues (Cont'd)

b) Use of Flora

Since the active ingredient methoxsalen is derived from wild flora, specific information regarding the source of the flora is discussed below.

1) Plant identification: *Ammi majus* (Umbelliferae)

2) Wild as well as cultivated plants have been used in support of this new drug application and will be used to produce the active ingredient, methoxsalen, in the future.

3) The *Ammi majus* plant grows wild and cultivated in several parts of Egypt. The plant is dense and more common along the banks of the Nile River in the northern delta region of Egypt.

4) Since the plant is considered a weed, there is no Egyptian government oversight or regulation of the harvesting.

5) The *Ammi majus* plant is not: (1) considered to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES); (2) entitled to special protection under some other Federal law or international treaty; or (3) the critical habitat of a species considered to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES).

6) The active ingredient methoxsalen is a naturally occurring photoactive substance found in the seed (fruits) of the *Ammi majus* plant. When the plant is ripe the fruits, which develop on the end of long umbels, are separated easily from the stalks by lightly tapping the umbels. Because only the seeds are used and the harvesting process does not damage or destroy the plant, the plant is a renewable resource.

7) The seeds of the *Ammi majus* plant are harvested using the process described above; consequently, the ecosystem is not affected. There are no Egyptian government regulations or guidelines regarding harvesting of the seeds.

8) It takes 500 kg of seeds (fruits) to produce 1 kg of methoxsalen drug substance. Approximately 375 kg of seeds has been harvested to date to support the proposed action.

6. Environmental Issues (Cont'd)

9) The dosing regimen for UVADEX methoxsalen Sterile Solution is 400 µg (two 200µg treatments) per patient. Consequently, it takes 0.0002 kg of seeds to produce methoxsalen drug substance to treat the average patient.

Cutaneous T-cell lymphoma (CTCL) affects approximately 0.4/100,000 persons. The anticipated maximum production level for methoxsalen drug substance based on the five-year (1998-2002) production average is one 57 g lot per year.

10) The *Ammi majus* plant grows wildly and abundantly in several areas of Egypt, particularly in the northern delta region of the Nile River. Therefore, it is difficult to provide an estimate of the total number of plants in the geographic region.

11) There are no uses of the plant other than for the proposed use.

12) It takes approximately six to eight months to grow a new, mature plant from seed.

7. Mitigation Measures

The active ingredient methoxsalen is a naturally occurring photoactive substance found in the seed (fruits) of the *Ammi majus* plant. When the plant is ripe the fruits, which develop on the end of long umbels, are separated easily from the stalks by lightly tapping the umbels. Because only the seeds are used and the harvesting process does not damage or destroy the plant, the plant is a renewable resource.

Photopheresis using oral crystalline formulations of methoxsalen has been approved in the U.S. and some European countries as extracorporeal photomedical therapy indicated for the palliative treatment of the skin manifestations of CTCL. However, a concern associated with oral methoxsalen is that its bioavailability is both variable and unpredictable. Approximately 20% of patients are found to have sub-therapeutic drug levels while others develop blood levels greatly more than what is considered necessary for optimal effect upon photoactivation. Such high drug levels increase the likelihood of systemic adverse reactions (mainly nausea and photosensitivity reactions). Because UVADEX methoxsalen Sterile Solution is administered extracorporeally, a much smaller amount of drug is required, and the methoxsalen concentration can be achieved very precisely with virtually no measurable systemic exposure to the drug. Consequently, the dosing regimen for methoxsalen capsules is 40 mg (0.6 mg/kg of body weight) compared to 200 µg for UVADEX methoxsalen Sterile Solution per treatment.

7. Mitigation Measures (Cont'd)

Thus, approval of UVADEX methoxsalen Sterile Solution will reduce the use of methoxsalen for the same indication as well as the environmental impact.

8. Alternatives to the Proposed Action

Reasonable alternatives to using the *Ammi majus* plant are limited since methoxsalen occurs naturally in the plant. One alternative is to produce methoxsalen using only seeds obtained from cultivated plants. However, the plant is difficult to cultivate and the wild variety produces more seeds (fruit). Furthermore, because only the seeds are used and the harvesting process does not damage or destroy the plant, the plant is a renewable resource

9. List of Preparers

This document was prepared by a consultant, Henry W. Fox, Jr., RAC. Mr. Fox has over 11 years experience preparing and assessing regulatory documents. He holds a B.Sc. in Chemistry and a M.Sc. in Pharmaceutics. A copy of his current curriculum vitae is attached.

10. References

Not applicable.