PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20969	**Trade Name:**	UVADEX (METHOXSALEN) 20 MCG/ML IV
Supplement Number:		**Generic Name:**	METHOXSALEN
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	UVADEX® Sterile Solution (methoxsalen) is indicated for use with the UVAR® Photopheresis 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.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

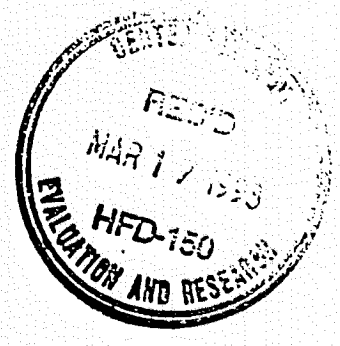
Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
The oral formulation of methoxsalen (Oxsoralen-Ultra Capsules) was approved for use with the UVAR Photopheresis System to treat CTCL in 1986 (HFD-540). This NDA 20-969 is a change in the formulation (Sterile Solution) to be administered extracorporeally. There is no pediatric clinical data in this application. DCatterson (2.23.99)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DEBRA CATTERSON

Signature /S/ _____ Date 2/23/99

THERAKOS
a Johnson & Johnson company



NDA # 20,969
UVADEX®
8-methoxypsoralen

FOR TREATMENT OF THE SKIN MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA

DEBARMENT CERTIFICATION

THERAKOS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306 (A) OR (B) OF THE ACT] IN CONNECTION WITH THE NEW DRUG APPLICATION FOR UVADEX LIQUID METHOXSALEN. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON, KNOWN TO BE DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT.

Signed: Peggy Schwartz Date: 3/12/98
Peggy Schwartz, Regulatory Affairs Manager

Oaklands Corporate Center, 437 Creamery Way, Exton, PA 19341

MEETING MINUTES

MEETING PURPOSE: NDA Status Team Meeting

NDA#: 20-969 **DRUG:** UVADEX® Sterile Solution (methoxsalen)

DATE: January 4, 1999 **TIME:** 12:00pm Conference Room B

CONTACT: Debbie Catterson (827-1544)

Uvadex Review Team **(Attendees in Bold):**

Medical:	**Isagani Chico, M.D.**
	Grant Williams, M.D. (Team Leader)
	Robert Justice, M.D. (Acting Division Director)
Chemistry:	**Yung-Ao Hsieh, Ph.D.**
	Rebecca Wood, Ph.D. (Team Leader)
Pharmacology:	David McGuinn, Ph.D.
	Paul Andrews, Ph.D.(Team Leader)
Biopharmaceutics:	**Atik Rahman, Ph.D.(Team Leader)**
Biometrics:	**Ning Li, Ph.D.**
	Gang Chen, Ph.D. (Team Leader)
Project Manager:	**Debbie Catterson, R.Ph.**

SUMMARY OF MEETING:

- Medical- Dr. Chico did not have any requests/comments for the sponsor at this time. He anticipates completing his review by the end of January 1999.

- Chemistry-Dr. Hsieh stated that his review is almost complete. He does have comments on the labeling that need to be sent to the sponsor by the project manager. Dr. Hsieh also noted that all of the chemistry consults (EER, EA, Micro., Trademark, and Stat. Stability) were completed and acceptable. However, we do need a copy of the completed Trademark consult from Dan Boring. (The project manager will take care of this.)

- Pharmacology-Dr. Andrews stated that he believes there are no issues at this time.

- Pharmacokinetics-Dr. Rahman is awaiting a response from the sponsor concerning PK data. If we do not receive the data by the end of this week, Dr. Rahman will complete his review and have the request for data as a Phase 4 commitment. Dr. Mehul Mehta will perform the secondary review.

- Statistics-Dr. Li stated that his review had been completed a month ago.

The review team discussed the target dates for completion of reviews and labeling comments and agreed to the following deadlines:

- ☞ Deadline for submitting labeling comments to the project manager - **JANUARY 25**
- ☞ Deadline for PM to incorporate all comments and circulate lab. to team - **JANUARY 27**
- ☞ Tentative Labeling Meeting (if needed) - **FEBRUARY 4**

PDUFA Due Date - February 25, 1999 - Dr. Justice to sign action letter.

ACTION ITEMS:

1. The project manager will forward the chemist's labeling comments to the sponsor.
2. The project manager will contact Dan Boring for a copy of the completed Trademark Consult.

cc:
Original NDA 20-969
HFD-150/Div File
HFD-150/IChico/GWilliams/YHsieh/RWood/WMcGuinn/PAndrews
/ARahman/NLi/GChen/DCatterson

Drafted by: DCatterson/1.4.99

CATERSON

MEDICAL OFFICER REVIEW FOR THE 45 DAY FILING MEETING (NDA 20-969)

FILING DATE:	February 25, 1998
DATE OF REVIEW:	April 9, 1998
SUBJECT:	Day 45 Report for NDA 20-969 (Uvadex)
FROM:	Isagani Chico, MD, Medical Officer

Uvadex (methoxalen) Sterile Solution is indicated for use with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell Lymphoma (CTCL). Currently, uvadex is approved as an oral capsule formulation in combination with UVA for the treatment of vitiligo, psoriasis and CTCL (PMA 86-0003 for CTCL approved by CDER in 1985).

A minimum plasma concentration of 50 ng/dl is required for activity; however, due to interindividual variability in pharmacokinetics after oral ingestion, the toxicity profile and activity of the drug have been unpredicatable. Two of three studies submitted to the NDA (CTCL 1 and CTCL 2) were on patients with who were given oral 8-MOP and subjected to photopheresis. Part of the data, including pictures of patients are cross-referenced to PMA-86-0003. The third study (CTCL 3) was done on 51 patients who received Uvadex + UVAR. The sponsor claims that Uvadex plus UVAR has equivalent efficacy compared to PUVA and that Uvadex + UVAR is better tolerated.

The NDA was submitted in 51 volumes. Clinical trial study reports were submitted for the three studies and an integrated summary of safety and efficacy. Case report forms were submitted for all patients who died within 30 days of last treatment and for drop-outs related to toxicity. Individual patient listings were submitted but was incomplete, based on the information that was available on the case report forms.

A teleconference was held between the applicant and the FDA on March 24 to discuss the electronic submission of the data. The sponsor has submitted the data in Paradox format but has agreed to submit the data in MS Access for the medical reviewers. The applicant will also provide annotated case report forms and an index to the electronic data.

COMMENTS:

On preliminary inspection, NDA 20-969 is adequate for review, assuming that the electronic data and the annotated case report forms will be submitted to the agency and also found to be adequate.

This application was designated a "S" (D21 meeting on March 21, 1998); drop dead date of February 25, 1999. If necessary, this application will be presented to ODAC in December, 1998.

Questions/Action Items (Medical):

1. Please ask the sponsor if a Premarket Approval Application (PMA) supplement has been submitted to the Center for Devices and Radiological Health (CDRH). For the FDA: Find out who the reviewers are and establish interaction. Provide them with a copy of our NDA review calendar and inquire about their review calendar.

2. Please secure a copy (or borrow?) of the Approval Package for PMA P86-0003 from CDER.

3. DSI Audit Consult: pending receipt of response from the sponsor regarding Item No. 3 (Requests to be sent to the sponsor by fax).

   Note: Data on CTCL 1 was included in PMA 86-0003 and may not need to be audited.

4. FDA Discussion: Since oral methoxalen +UVA is approved for the treatment of cutaneous T-cell lymphoma, vitiligo and psoriasis, discuss whether a separate label would be advisable for this new method of drug delivery. If this application is approved, does the sponsor intend to withdraw the indication for PUVA using oral methoxalen in CTCL?

Please send the following requests to the applicant by facsimile:

1. Please submit a revised version of the label containing the clinical data (i.e. a summary of efficacy and safety data on the three pivotal trials for CTCL plus additional safety data from other studies using the methoxalen + UVAR system).

2. Please submit a strikethrough version of the proposed label showing the changes that were made on the original label for 8-MOP (oral methoxalen). Parts of the label that are omitted or revised should be shown clearly and explained, if necessary.

3. If possible, please submit the following in a word processing format (preferably MS Word) :
   - Strikethrough Version and Proposed Final Labeling
   - Overall Summary of Safety and Efficacy
   - Individual Study Reports (CTCL1, 2 and 3)

4. Please provide the agency with a table containing the following data for each of the three studies:
   - Treatment Site/s
   - Location
   - Investigator's Name
   - Number of Patients Enrolled in the Site
   - Number of Patients Enrolled in the Site who Responded to Treatment
   - Period of Enrollment in Each Site, Period of Enrollment in Each Study

/S/

4/9/98

Isagani Mario Chico, M.D.
Medical Officer
Division of Oncology
HFD-150

5/1/98

cc: 20-969
Orig. NDA ~~#50-971~~
HFD-150/Division File
HFD-150/I.M. Chico, M.D.
HFD-150/Catterson

CAlkerson

Memo:	**45-day filing review**
Subject:	**NDA 20-969, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**
Submission Date:	February 20, 1998
Drug Name:	Uvadex (8-methoxypsoralen)
Formulation & Strength:	20 mcg/ml, sterile solution
Sponsor:	Therakos, Inc. 437 Creamery Way Exton, PA 19341
Reviewer:	Z. John Duan, Ph.D.
Type of Submission:	New Drug Application

BACKGROUND

Methoxsalen (8-methoxypsoralen) is a member of the group of compounds known as psoralens or furocoumarins. Methoxsalen is a naturally occurring compound which is present in many plants, including food plants such as citrus, parsley, celery and figs. The pharmaceutical product available in the United States is a synthetic compound with the chemical name 9-methoxy-7H-furo(3,2-g)(1)bezopyran-7-one. Methoxsalen is a photosensitizing agent with preferentially accumulates in epidermal cells. Methoxsalen is usually used in combination with ultraviolet light activation, a treatment known as PUVA (psoralen plus ultraviolet light A). Upon photoactivation, methoxsalen forms covalent bonds with DNA leading to inhibition of DNA synthesis, cell division and epidermal turnover.

Methoxsalen (8-MOP, ICN; NDAs 09-048, 19-660) is approved in the United States for oral use in the treatment of severe, recalcitrant psoriasis, for repigmentation of idiopathic vitiligo, and for the treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL). Treatment of psoriasis and vitiligo are approved as PUVA (psoralen plus ultraviolet light A). Treatment of CTCL is currently approved under a Premarket Approval Application (PMA P860003) as photopheresis. Photopheresis is the collection and exposure of extracorporeally circulating leukocyte-enriched blood to long-wave ultraviolet (UVA) energy in the presence of the photoactive drug.

UVADEX was developed for extracorporeal use in conjunction with the UVAR photopheresis system. This new dosage form should permit the delivery of a standardized concentration of methoxsalen directly to the extracorporeal blood volume. Systemic exposure to methoxsalen will be reduced, thus reducing or potentially eliminating the side effects of nausea and sunlight sensitivity. UVADEX sterile solution is indicated for use with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma in patients who have been unresponsive to other forms of treatment.

No new pharmacokinetic studies have been conducted to support this NDA. The studies provided are published reports of the human kinetics and bioavailability of orally and intravenously administered methoxsalen.

Section 6 of the NDA contains 11 publications, five of which are listed in the **Appendix**. These five studies evaluated the pharmacokinetics and metabolism of methoxsalen. One of these studies investigated the kinetics and distribution of methoxsalen following intravenous administration. The other four studies compared the kinetics and distribution of methoxsalen following administration as tablets, capsules or oral solutions. One study compared tissue levels of methoxsalen to those determined in plasma.

During the Uvadex CTCL clinical trial, patient serum concentrations of methoxsalen were measured post-reinfusion of the treated cells. However, this study was not included in Section 6 of the NDA. Requested by Division of Pharmaceutical Evaluation I, the sponsor specified the location of the study in volume 24 and 25.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of this NDA appears to be filable from Clinical Pharmacology and Biopharmaceutics perspective.

/S/

Atiqur Rahman, Ph.D. — 4/9/98 Date

Team Leader
Division of Pharmaceutical Evaluation I

/S/

Z. John Duan, Ph.D. — 4/8/98 Date

Reviewer
Division of Pharmaceutical Evaluation I

20-969 DC

CC: NDA ~~20798~~ original
HFD-150 Division File
HFD-150 DCatterson
HFD-150 IChico
HFD-850 LLesko
HFD-860 HMalinowski, MMehta, ARahman, JDuan
CDR Barbara Murphy