

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-415

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD-540

23 JULY 2002

NDA: 21-415 BC

Drug Product Name

Proprietary: Metvix

Non-proprietary: 5-Aminolevulinic Acid

Drug Product Classification: S

Review Number: 1

Subject of this Review

Submission Date: 6 June 2002

Receipt Date: 6 June 2002

Consult Date: 6 June 2002

Date Assigned for Review: 12 June 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): 26 September 2001

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Photocure ASA

Address: Hoffsvæien 48, N-0337, Oslo, Norway

Representative: William A. Clementi, Pharm.D.

Telephone: 610-581-7021

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: N/A
 2. SUPPLEMENT PROVIDES FOR: N/A
 3. MANUFACTURING SITE:
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Cream for topical administration, 168 mg/gram
 5. METHOD(S) OF STERILIZATION: N/A
 6. PHARMACOLOGICAL CATEGORY: Non-hyperkeratotic actinic keratoses
- B. SUPPORTING/RELATED DOCUMENTS: N/A
- C. REMARKS: N/A

filename: 21415.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is a non-sterile, preserved, topical cream.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – The drug product has appropriate — specifications for a topical product and is adequately preserved. The drug product therefore presents a low risk to public health from the standpoint of product quality microbiology.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Peter H. Cooney, Ph.D. (Microbiology Supervisor)
- C. CC Block**
N/A

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bryan Riley
8/12/02 09:49:13 AM
MICROBIOLOGIST

Peter Cooney
8/12/02 11:32:05 AM
MICROBIOLOGIST

**Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1
Consult**

NDA # 21-415

Date Completed: May 7, 2002

Applicant (NDA): Photocure ASA
Hoffsveien 48
N-0377 Oslo
Norway

Chem/Ther. Type: Fatty acid derivative, Keratolytic

Submissions Reviewed: Amendment to a pending Original New Drug Application

Providing for: A light measuring diode device used for calibration prior to illumination with PhotoCure Halogen PDT Lamp for treatment of actinic keratosis with Metravex® Cream.

Product Name(s):

Proprietary: Metravex® Cream

Non-proprietary: 5-Aminolevulinic Acid

Code name/number: P-1202

Chemical name: 5-Aminolevulinic Acid

Dosage form(s): Cream, 168 mg/g Plus PhotoCure Halogen PDT Lamp 570-670 nm
Route of administration: Topical(Cream) plus illumination

Pharmacological Category: Keratolytic for Actinic Keratosis

Dispensed: Rx

Supplements/Amendments:

Received by CDER: 26-Mar-22002

Received by Reviewer: 4/3/02

Review Completed: 5/6/02

Related Documents: None listed

Remarks:

Consultative review NDA 21-415
5-Aminolevulinic Acid (Metvix®) plus photocure PDT Lamp
Sponsor: Photocure ASA Oslo, Norway
Joel Unowsky Microbiology reviewer (HFD 520)
Requesting Division: Dental and Dermatologic Drug Products (HFD 540)
CSO Vickey Lutwak
Reviewer: Brenda Vaughan
PDUFA Desired Completion Date: 7/26/02

Comments/Special Instructions:

Brenda Vaughan, M.D. is the reviewer.

“A light diode device is being used for calibration prior to illumination with Halogen PDT Lamp for treatment of actinic keratosis with Metvix® Cream. This diode device is placed directly upon skin which has been subject to curettage (with possibility of slight bleeding). -The Sponsor’s plan (Section 8, pg. 15 for
According to the User Manual (pg. 11), calibration should be performed with the light measuring diode placed at the lesion surface prior to illumination. There is a concern that lesion preparation might produce an open wound and some bleeding since lesion preparation consists of debriding with a small dermal curette to remove scales, crusts, and to roughen the surface. Metvix® Cream is then applied to the prepared lesion and covered with an occlusive dressing for 3 hours. The surface area is cleaned with saline and gauze prior to calibration with the light measuring diode and illumination.”

Question for the microbiology reviewer: Is the Sponsor’s plan adequate for between patient disinfecting of the light measuring diode?

The following statement on page 8 of the user Manual is the only instruction concerning sterilization:

I find both the instructions and method of disinfecting the light measuring diode inadequate because of the following considerations:

Methods for the establishment of sterility testing and standards is the responsibility of the, "Sterility Products Working Group of the CMC CC" within the Office of Pharmaceutical Sciences. Dr. Peter Cooney is the supervisory microbiologist for the group and can be contacted at 301-827-7340, HFD 805-18B08 Parklawn building.

Conclusions/Recommendations:

The method of diode sterilization is unsatisfactory. It is recommended that Dr. Peter Cooney be contacted to aid in the establishment of satisfactory methods for sterilization of the diode in order to protect the patients from exposure to pathogens on their open wounds

Joel Unowsky
Microbiology Reviewer

File name: Metravex® Cream

SMicro/ATSheldon
RD#1 and Final Initialed 5/7/02 ATS
DepDir/LGavrilovich

Cc: Original NDA # 21-415
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro/JUnowsky
HFD-540/MO/BVaughn
HFD-540/CSO/VLutwak
HFD-540

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joel Unowsky
5/7/02 10:40:54 AM
MICROBIOLOGIST

Albert Sheldon
5/7/02 10:51:07 AM
MICROBIOLOGIST

Lillian Gavrilovich
5/9/02 04:10:46 PM
MEDICAL OFFICER

Clinical Pharmacology/Biopharmaceutics Review

NDA:	21-415
SUBMISSION TYPE:	Complete Response to Approvable Letter Items
SUBMISSION DATE:	5/27/2004
PRODUCT:	Methylaminolevulinate 168 mg/g cream TRADENAME cream
SPONSOR:	PhotoCure ASA, Norway
US AGENT:	Clementi King Assoc., PA
INDICATION:	Actinic Keratosis
REVIEWER:	Tapash K. Ghosh, Ph.D.
Acting TEAM LEADER:	Arzu Selen, Ph.D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 540

Background

In this Type I resubmission, the Sponsor has provided a draft final labeling, a safety update and a restatement of their Phase IV Commitments.

One of the two Phase IV studies the Sponsor has agreed to conduct is an in vivo bioavailability study. The Sponsor is indicating that the protocol development for this study is underway, and is clarifying the additional information that will be included in the study protocol.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, in general terms, finds the Sponsor's proposed Phase IV study acceptable and recommends the following:

- In the bioavailability study, a range of concentrations of methyl aminolevulinate cream (preferably, 80, 120 and 168 mg/g) should be applied and the study should be conducted in patients who have multiple (8 – 10) actinic keratosis lesions.
- The amount of TRADENAME Cream used (number of tubes and amount used from each tube) as well as the total body surface area in cm² treated for each patient should be provided.

The following timelines are acceptable:

Protocol Submission: August 2004
Study Start: January 2005
Final Report Submission: December 2006

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III

Acting Team Leader: Arzu Selen, Ph.D. _____ Date _____
Deputy Division Director, Division of Pharmaceutical Evaluation III

Clinical Pharmacology/Biopharmaceutics Review

NDA:	21- 415
SUBMISSION TYPE:	Complete Response to Approvable Letter Issues
SUBMISSION DATE:	July 17, 2003
PRODUCT:	Methyl aminolevulinate 168mg/g Cream
INDICATION:	Actinic Keratosis
SPONSOR:	PhotoCure ASA, Norway
US AGENT:	Clementi Associates, PA
REVIEWER:	Tapash K. Ghosh, Ph.D.

Background:

While the Sponsor did conduct a number of in vivo biopharmaceutics studies as part of their original NDA, the studies themselves did not, in the Agency's opinion, demonstrate in a definitive manner that the 168 mg dosing regimen was the optimal regimen. Part of the problem is evaluating the results from the original trial related to the wide separation of doses, i.e., 16 and 80 mg/gm. Examination of the data from the original NDA showed that the 80 mg/gm treatment showed significant activity such that an intermediate dose between 80 and 160 should have been investigated, i.e. 100 or 120 mg/gm.

The sponsor proposed to conduct a Phase 4 study to address the above issue. A synopsis of the proposed Phase 4 study has been submitted along with for Agency's review.

Synopsis of Proposed Phase 4 Study:

Purpose:

1. To assess the systemic bioavailability after application of methyl ALA cream of different concentrations in wide spread AK.
2. To assess the build up of photoactive porphyrins(PpIX) after application of methyl ALA cream of different concentrations in wide spread AK.

Population: Approximately 24 patients with multiple (8 – 10) AK lesions.

Design: Patients will be randomized to 4 treatment groups to receive treatment of all eligible AK lesions with concentrations of 80, 120 and 168 mg/g methyl ALA cream for 3 hour before illumination. Lesions will be prepared as in other clinical trials.

Primary endpoints: Plasma concentrations of ALA and PpIX before cream application and after 3 h cream application immediately before illumination.

Secondary endpoints: Fluorescence per lesion before and after 3 h cream application immediately before illumination. Systemic bioavailability at different doses of methyl ALA (amount of cream at different concentrations).

Analytical Methods: An analytical method for ALA in human plasma will be validated prior to use in this study. The validated analytical method for detection of PpIX fluorescence from a surface used in Study PC T214/01 will be used in the proposed study.

Comments: The sponsor's proposal to conduct a Phase 4 study as per request of the Agency in the Clinical Pharmacology and Biopharmaceutics section is acceptable. The synopsis of the study appears to meet the purpose of the study. However the Agency will look forward to the complete protocol which should definitely include amount of methyl ALA (number of tubes and amount used from each tube) used as well as surface area used for each patient.

Tapash K. Ghosh, Ph.D.
Pharmacokineticist, DPE III

Team Leader: E. Dennis Bashaw, Pharm.D. _____

CC: NDA 21-415; HFD-540/Div File; HFD-540/CSO/Harris; HFD-880(Bashaw/Ghosh);
HFD-880 (Lazor/ Selen); To DFS

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tapash Ghosh
10/23/03 05:51:50 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/24/03 03:25:56 PM
BIOPHARMACEUTICS