

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-415

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-415

PhotoCure, ASA
Attn: William Clementi, Pharm.D., F.C.P.
161 Washington Street
8 Tower Bridge, Suite 1045
Conshohocken, PA 19428

Dear Dr. Clementi:

Please refer to your new drug application (NDA) dated September 26, 2001, received September 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (methyl aminolevulinate) Cream, 16.8%, in combination with the CureLight BroadBand Model CureLight 01, which was submitted under premarket approval application (PMA) P010061.

We acknowledge receipt of your submissions dated July 16, 23, and 24, August 19, October 2 and 30, November 21 (2), December 2, 12 (2), and 15, 2003.

The July 16, 2003, submission constituted a complete response to our September 19, 2002, action letter.

We also acknowledge receipt of your submission dated December 16, 2003. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable pending approval of the CureLight BroadBand Model CureLight 01. The Center for Devices and Radiological Health (CDRH), Division of General, Restorative and Neurological Devices will convey deficiencies for the CureLight BroadBand Model Curelight 01. In addition, before the application may be approved, it will be necessary for you to:

- 1) Conduct an in vivo biopharmaceutics study to assess the systemic bioavailability after application of methyl aminolevulinate cream of different concentrations in wide spread actinic keratosis. Please revise your submitted protocol to include 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.
- 2) Conduct a 12-month safety study in at least 200 evaluable patients with 10 or more actinic keratosis lesions with diameters of ≥ 4 mm, documenting the effects of retreatment of lesions with partial response and treatment of new lesions. In this study, representative numbers of patients with higher

Fitzpatrick skin types, e.g. Asians and Hispanics, should be included. Location of lesions should be sufficiently identified for long-term follow-up. The gram amount of TRADENAME Cream applied with each treatment session should be documented. Laboratory parameters should be collected, and patients should be monitored for photoallergic skin reactions.

In addition, it will be necessary for you to submit draft labeling revised in accordance with the enclosed labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Dermatologic and Dental Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Melinda Harris, M.S., Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug
Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

19 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Stanka Kukich

1/16/04 01:33:35 PM

Signing for Dr. Jonathan Wilkin



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-415

Photocure ASA
Attention: William A. Clementi, Pharm.D.
919 Conestoga Road
Rosemont, PA 19010

Sept. 19, 2002

Dear Dr. Clementi:

Please refer to your new drug application (NDA) dated September 27, 2001, received September 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (methyl aminolevulinate) Cream, 16.8%, in combination with 570 to 670 nm wavelength red light illumination using the CureLight BroadBand Model CureLight 01 lamp.

We acknowledge receipt of your submissions dated October 30, November 6, 13, and 14, and December 12 and 19 (two), 2001; January 17, February 20 and 28, April 2, 5, 7, 12, 16, 18, 19, and 26, May 3, 6, 23, 24, and 28, June 6, 11, 27, and 28, July 17, 18, 24 and 30 and August 5 and 8, 2002; facsimile transmissions dated October 16, 22, 25, and 30, 2001; February 21 (two), March 22, and July 19 and 23, and September 12, 2002; and an electronic mail dated June 6, 2002.

This new drug application is submitted to support the use of TRADENAME (methyl aminolevulinate) Cream, 16.8% in combination with 570 to 670 nm wavelength red light illumination using the CureLight BroadBand Model CureLight 01 lamp for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp.

We have completed the review of this application, as amended, and it is approvable. Please submit draft labeling revised in accordance with the enclosed labeling. Further discussions regarding the labeling may be necessary.

Deficiencies to be addressed:

Chemistry, Manufacturing and Controls:

In addition to the changes in the draft package insert accompanying this letter, please make the following changes for the carton and container:

Add the following information:

- Product Package
- Keep out of reach of children
- For dermatologic use only
- Rx Only

Storage Conditions

Store refrigerated, 2-8°C (36-46°F).

Use contents within one week after opening.

Change the following:

The company logo should be reduced to the same size as the Proprietary Name's font size.

Cream will be capitalized and placed after TRADENAME followed by the 16.8%, e.g., TRADENAME Cream, 16.8%.

Pharmacology/Toxicology:

Tissues collected in the repeated dose dermal toxicology study in minipigs should be evaluated histologically.

Biopharmaceutics:

At this time the applicant has not adequately assessed the in vivo bioavailability of methyl-levulinic acid or levulinic acid (the active form of methyl-levulinic acid). A new in vivo bioavailability study, using both a validated analytical method and proper site preparation procedures (consistent with those used in the clinical trials) should be conducted using the clinical dose of Metvix Cream.


Based on the submitted data, it is not possible to determine whether the dose and conditions are optimized. That is, the reasoning for selection of the 168-mg/gm dose and the application time (period from application of the cream to photo-activation) is unclear. It is possible that a lower dose under optimized conditions may provide equal or more benefit than the 168-mg/gm dose. Should additional clinical trials be initiated in support of this application, then the applicant should be encouraged to re-evaluate the safety and efficacy of lower doses.

Clinical:

Efficacy has been demonstrated in two clinical trials with use of two treatment sessions of Tradename Cream-PDT over vehicle cream-PDT in treatment of actinic keratosis of the face and scalp when used as supplementary to curettage. From a clinical perspective, the application is *Approvable*; however, there are multiple concerns that are either unresolved or were not adequately addressed by the Sponsor in the submitted dataset.

The quality and quantity of the safety database submitted with the NDA application does not include enough information to exclude possible safety issues for the proposed dosing regimen. New data submitted for the first time at NDA submission and new information resulting from queries made by the Division during NDA review have made it evident that additional safety data is needed prior to approval while other informational needs can be derived from Phase 4 studies.

It is determined that the safe use of TRADENAME cream would need both the conditions placed in the enclosed draft labeling and the following informational needs that the Sponsor must adequately address prior to approval:

- 1) Conduct an adequate 21-day contact sensitization potential study of methyl-ALA, employing in the challenge phase test both ALA which is an endogenous metabolite (to rule out cross-sensitization) and methyl-ALA.
- 2) Provide data driven instructions for prevention of sensitization of healthcare professionals handling TRADENAME cream.
- 3) Develop visual instructional material (e.g., video, CD, etc.), as part of labeling, to ensure the safe and effective use of the drug-device. The material should not be promotional in nature and should be submitted to the Agency for approval prior to distribution. The instructional material should include (but not be limited to) dosage and administration procedures. Adequate procedures to prevent cross contamination with between patient use of the device are also needed.
- 4) The Sponsor's Package Insert was modified in the enclosed draft labeling to provide information for the practitioner addressing safety concerns and information needed for use of this drug product. Provide the following additional information needed for the Package Insert:
 - A. Identify types of gloves which methyl-ALA and excipients found in TRADENAME Cream will not penetrate.
 - B. Submit the line listings and serum transaminase level information for the patients treated with TRADENAME Cream in the BCC study(ies).
 - C. Describe the lack of safety monitoring in Phase 3 studies to evaluate the potential for systemic adverse events for signals found in preclinical studies.
 - D. Provide the maximum duration of time permissible between application and illumination. Please provide information regarding needed adjustments to duration of light treatment following inadvertent prolonged exposure to TRADENAME Cream before light exposure. Provide information regarding what a patient should do if there is prolonged exposure without subsequent light treatment - e.g. avoidance of sunlight for how many days. All of these pieces of information should be supported with data.
 - E. Modify labeling so that patients are instructed to rinse off cream when left on for longer application periods than supported by data and to avoid illumination to the treated area(s). It is unknown whether the risk of illumination after longer application periods (e.g., with

TRADENAME Cream is warranted for the treatment of actinic keratosis.

- F. Provide instructions for what should be done with light overexposure. This may be similar to management of burns from other causes.
- G. Submit a Patient Package Insert to describe to patients the details and the safety aspects of the PDT procedure with TRADENAME Cream.
- H. Provide information regarding the radiant heat and temperature achieved with skin surfaces exposed to the Curelight Model 01 device. This information should also be provided to the CDRH device reviewer.
- I. Provide information and rationale regarding how long the redness and swelling should last before the patient should contact their doctor. This should be supported with data from studies.
- J. Provide data regarding how long it takes for the surrounding skin reddening, swelling, crusting, blistering, edema, ulceration, peeling, itching and bleeding to resolve.
- K. Provide data regarding actual percentages of patients with peeling, bleeding, itching and severe pain in patients aged 65 and older (being greater than that in younger patients).
- L. Provide the proportion of patients treated with TRADENAME Cream with adverse events. The denominator for adverse events should not be diluted with vehicle or other treatments.
- M. Provide the percentages and proportions for adverse events based on occurrence(s) per patient.
- N. Provide information regarding severity of burning sensation and skin pain seen in U.S. and Australian studies.
- O. Identify the light transmittance through 1 millimeter of TRADENAME Cream at 30°C.
- P. Provide a list of anesthetics and the frequency with which they were used in Phase 3 studies.
- Q. Identify the type of spatula used in clinical studies (e.g. what is the composition?).
- R. Provide subgroup analysis with regard to wait time or information regarding compensatory calculations for lamp exposure during CureLight 01 light treatment.
- S. Provide explicit procedures for use of the device (CureLight 01 lamp) that would allow for adequate patient protection and prevent cross-contamination (i.e., Universal Precautions), yet at the same time, not hinder effective use.
- T. Provide information/description for treatment of multiple actinic keratosis lesions in one treatment session (
- U. Provide information regarding effect of local anesthesia and increased pain intolerance on adverse events (i.e., were patients who were given local anesthesia more likely to have burns due to failure to feel discomfort and/or were they less likely to report local adverse events such as pain and stinging?).
- V. Provide information regarding what should be done with the lesion area after exposure to red light treatment with the CureLight 01 lamp.
- W. Submit a visual aid that will be part of labeling. The treatment process appears

to be fairly complicated and such an aid should allow for safer (for both practitioner and patient) and more effective use of your drug/device.

X. Provide information on both light and drug overdosage that are supported by data.

Y. Identify if _____ is appropriate to be placed under _____

- 5) Submit the clinical trial results of Study PC T212/00 which is a Phase 2 randomized, comparative phototoxicity study of TRADENAME cream vs. ALA 20% cream applied for 5 hours conducted in healthy individuals. Submit a complete safety update including all safety data from other studies conducted with TRADENAME cream.
- 6) Commit to conduct the following Phase 4 post-marketing studies:
 - A. A clinical 12-month study in at least 200 evaluable patients with 10 or more lesions (located on the face and scalp) in whom the following are collected: hepatic transaminases (ALT and AST), alkaline phosphatase, total bilirubin, and complete blood count plus differential data both at baseline and at one week after the second repeat dose 7-day regimen.
 - B. A longer-term clinical study documenting the effects of multiple retreatments and recurrence rate with this product. Actinic keratoses may be considered to be a chronic intermittent disease and multiple retreatments are common, especially in older, sun-overexposed patients.
 - C. A clinical dermal safety study to determine the photoallergenicity potential of TRADENAME Cream with a diluted form of TRADENAME Cream.
 - D. A safety and efficacy Phase 4 study of TRADENAME Cream in patients of Asian and in patients of Hispanic heritage.
- 7) Provide the following informational needs previously requested by the Agency. During conduct of the Phase 3 studies:
 - A. Was there any patient discomfort associated with lesion preparation (for example with curettage)?
 - B. Did the investigators use anesthetics prior to lesion preparation?
 - C. Did the investigators use gloves during TRADENAME Cream application?
 - D. Were there any personnel protection instructions for inadvertent exposure to TRADENAME Cream?
 - E. Is Tegaderm® transparent or translucent, and what instructions were given to patients regarding restrictions during the 3-hour interval between TRADENAME Cream application and removal?
 - F. Did patients experience any adverse events (e.g., burning, stinging, itching, etc.) during TRADENAME Cream application prior to removal? If so, what were the treatments given for such adverse events?
 - G. What instructions were provided regarding use of 2 lamps? Was there a strategy developed for cream removal, avoidance of overlapping treatment fields, etc.? Was there a limit to the number and location of treatment fields?
 - H. What was the purpose for use of water spray and fan during illumination? Was this technique included in the protocol? What type of water spray was used and would use of a water spray disperse residual TRADENAME Cream?
 - I. Since the Sponsor did not provide disinfection/sterilization procedures, what infection control techniques were employed by the investigators for between patient use of the

device?

- J. Did the study nurse follow a triage protocol for referral to the sub-investigator for treatment of local adverse events?
- K. Who recorded local and systemic AEs at the following:
 - before and after each treatment session,
 - at 2 week post-treatment visit, and
 - 3-month efficacy endpoint visit?
- L. Were there post-treatment instructions provided for patients (e.g., restrictions immediately after treatment, remedies for possible adverse events such as swelling, burning, crusting, etc.).

Additional Comments:

The proposed name of “Metvix” has been found to be not acceptable by Agency reviewers in the Office of Drug Safety. You will need to propose a new TRADENAME for review prior to marketing this product. The product, when and if approved, may still have this issue outstanding.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
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4. Provide case report forms and narrative summaries for each patient who died during a

clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate for use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Victoria Lutwak, Project Manager, at (301) 827-2073.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic &
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

14 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 + § 552(b)(5) Deliberative Process

 J § 552(b)(5) Draft Labeling