DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-415/S-003

Cato Research for Photocure, ASA
Attention: William Lee, Ph.D., R.A.C., Senior Regulatory Scientist
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Dr. Lee:

Please refer to your supplemental new drug application dated June 27, 2007, received June 28, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for a combination product comprised of Metvixia (methyl aminolevulinate hydrochloride) Cream, 16.8%, and the CureLight BroadBand Model CureLight 01 lamp.

We acknowledge receipt of your submissions dated October 24, 2007; and January 2, February 13, April 9, April 23, April 24, May 9, May 13, May 15, June 10, and June 23, 2008.

This supplemental new drug application provides for the use of Metvixia (methyl aminolevulinate hydrochloride) Cream, 16.8%, in combination with the new Aktilite® CL128 lamp for the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratoses of the face and scalp in immunocompetent patients.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We remind you of your March 21, 2005 commitment to withdraw [redacted] for the CureLight lamp upon approval of the combination product comprised of Metvixia (methyl aminolevulinate hydrochloride) Cream, 16.8% and the Aktilite® CL128 lamp.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved supplement NDA 21-415/S-003.**"

LAMP OPERATOR'S MANUAL

As soon as possible, but no later than 14 days from the date of this letter, please submit the Operator's Manual in SPL format that is identical to the enclosed Operator's Manual. Upon receipt, we will

transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved supplement NDA 21-415/S-003.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission, "**Final Printed Carton and Container Labels for approved supplement NDA 21-415/S-003**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have requested a waiver of this requirement. This application does not require pediatric studies under PREA. Therefore, a waiver is not necessary.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitments in your submission dated May 9, 2008. These commitments are listed below.

1. Conduct a systemic bioavailability study using a properly validated assay method to measure methyl aminolevulinate and metabolite (aminolevulinic acid) in plasma under the labeled condition of use in subjects with multiple (8-10) actinic keratosis lesions. Revise your submitted protocol to include the amount of methyl aminolevulinate cream used and include the total body surface area in square centimeters treated for each subject.

Protocol Submission:	by September 1, 2008
Study Start:	by January 2, 2009
Final Report Submission:	by January 2, 2011

2. Conduct a clinical study to evaluate recurrence or partial response to treatment in patients treated with Metvixia/Aktilite PDT.

   Study length: A minimum of one year follow-up for recurrence of actinic keratosis for each subject.

Study design: To be proposed by PhotoCure and reviewed by the Agency prior to conduct.

Study population: Conduct this study in at least 300 evaluable Metvixia-Aktilite treated subjects with at least 5 actinic keratoses each at baseline. Initial enrollment should take into account expected drop out rate to achieve the pre-requisite numbers of evaluable subjects after one year.

Observation and Follow-up: Every 3 months for the first year of the study.

Study reports and Statistical Analysis: Descriptive analysis of recurrence rates for the first year together with assessment of safety.

Draft protocol:	by July 1, 2008
Initiate study:	by December 1, 2008
Complete recruitment:	by December 1, 2009
Complete study report:	by June 1, 2011

Submit clinical protocols to your IND for this combination product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol,**" "**Postmarketing Study Commitment Final Report,**" or "**Postmarketing Study Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this combination product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). FDA expects that your reports and postapproval supplements will apply to the entire combination product and its constituent parts under this application. All information should be submitted to CDER, Central Document Room. Further, postmarketing safety reports for the lamp would include: 1) a device event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health; and 2) a device malfunction that did not cause a patient adverse event but would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

If you have any questions, call Maria Walsh, Project Management Officer, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Daniel A. Shames
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