

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-415

**ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE**

PATENT INFORMATION

The patent number for the subject of this NDA, Metvix® 168 mg/g cream, is 6,034,267 and will expire on 8 March 2016. The patent is owned by PhotoCure ASA, Norway. The U.S. Agent for the patent owner is Clementi & Associates, Ltd.

The undersigned declares that Patent No. 6,034,267 covers the method of use of Metvix® cream, the subject of this NDA.



William A. Clementi, Pharm. D., F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent for Photocure ASA

21 September 2001

PATENT CERTIFICATION

Certification under 21 CFR 314.50(i)(B)(ii)

In the opinion and to the best knowledge of PhotoCure ASA, there are no patents (except PhotoCure's patent) that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Certification under 21 CFR 314.53(c)(3)

The applicant certifies that there are no patents, currently, which claim the drug or the drug product.

Declaration under 21 CFR 314.53(d)

The applicant declares that if a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the issuance of the patent, submit the required patent information in an amendment to the application under 21 CFR 314.60.



William A. Clementi, Pharm. D., F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent for Photocure ASA

21 September 2001

EXCLUSIVITY SUMMARY for NDA # 21-415 SUPPL # N/A

Trade Name TRADENAME Generic Name methyl aminolevulinate

Applicant Name PhotoCure HFD-540

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-965 Levulan Kerastick (aminolevulinate acid gel)

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A / X / YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

Submission regarding safety YES /_X_/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PC 306/99

Investigation #2, Study # PC 305/99

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # PC 306/99

Investigation # 2 , Study # PC 305/99

Investigation # , Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency,

or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 PC 306/00 (U.S.) !
IND # 59,765_ YES /_X_/! NO /___/ Explain:
!
!
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A !
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

Investigation #2 PC 305/99 !
YES /_X_/ Explain _____ ! NO /___/ Explain _____
!

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Jonathan Wilkin
7/27/04 04:20:28 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-415 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 7/17/03 Action Date: 1/17/04

HFD -540 Trade and generic names/dosage form: TRADENAME (methyl aminolevulinate) Cream, 16.8% in combination with the CureLight BroadBand Model CureLight 01

Applicant: PhotoCure ASA Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of non-hyperkeratotic actinic keratosis of the face and scalp

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

Handwritten signature: JW 2/22/04

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melinda J. Harris, M.S.

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

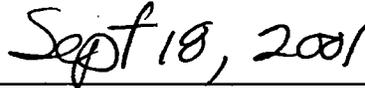
Melinda Harris
1/14/04 11:52:11 AM

Brenda Vaughan
1/14/04 04:16:45 PM

Stanka Kukich
1/15/04 08:56:45 AM

DEBARMENT CERTIFICATION

I, the undersigned, hereby certify that PhotoCure ASA did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this NDA application.

 : 

William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates Ltd

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-415	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: TRADENAME (methyl aminolevulinate) Cream, 16.8% in combination with the Curelight Broadband Model Curelight 01		Applicant: Photocure ASA
RPM: Melinda Harris, M.S.	HFD-540	Phone # 301-827-2020
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>N/A</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	keratolytic	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 	N/A	
❖ User Fee Goal Dates		
July 27, 2004		
❖ Special programs (indicate all that apply)		
<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	<input type="checkbox"/> Paid UF ID number	
<ul style="list-style-type: none"> • User Fee waiver 	<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
<ul style="list-style-type: none"> • User Fee exception 	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

<ul style="list-style-type: none"> This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> OC clearance for approval 	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) () Verified
	21 CFR 314.50(i)(1) () (ii) () (iii) N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	(X) N/A (no paragraph IV certification) () Verified
	() Yes () No
	N/A
	() Yes () No
	N/A
	() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

N/A

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

N/A

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	X No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE 1/16/04; AE 9/19/02
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	July 27, 2004
• Original applicant-proposed labeling	May 25, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS name review 6/21/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	May 25, 2004
• Reviews	May 25, 2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	July 20, 2004
• Documentation of discussions and/or agreements relating to post-marketing commitments	July 21, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	PIND/EOP2 June 22, 2000
• Pre-NDA meeting (indicate date)	May 2, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	July 27, 2004
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	July 27, 2004
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	July 27, 2004
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	January 16, 2004
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	July 27, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	N/A
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	N/A
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: July 25, 2002 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	June 24, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V**

FACSIMILE TRANSMITTAL SHEET

DATE: July 27, 2004

To: Dr. Kenneth King	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 19

Comments: Please find following the revised label with highlight/strikeout. If this is acceptable please fax a letter back stating the changes are acceptable and include the label. Please also submit this formally to the NDA.

Thanks,
Melinda

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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14 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ ___ § 552(b)(5) Draft Labeling

**CLEMENTI-KING**

Global Regulatory Affairs

8 Tower Bridge, Suite 1045
161 Washington Street
Conshohocken, PA 19428
regulatoryaffairs.com**VIA FEDERAL EXPRESS and FACSIMILE**

July 21, 2004

Jonathan Wilkin, MD, Director,
Division of Dermatologic and Dental Drug Products
HFD-540, ODE V, CDER
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 29854**RE: Phase 4 Commitments**
PRODUCT: PMA – P010061**SPONSOR: PhotoCure ASA, Oslo Norway, Clementi-King, Ltd. U.S. Agents**

Dear Dr. Wilkin:

PhotoCure ASA commits to conduct the following studies in the timeframe outlined below:

1. Conduct a systemic bioavailability study following application of methyl aminolevulinate cream with different concentrations ranging between 80 and 168 mg/g (preferably 80, 100, 120, 140 and 168 mg/g) in patients with multiple (8 – 10) actinic keratosis lesions. We will revise our 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.

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

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, will be included. Location of lesions will be sufficiently identified for long-term follow-up. The gram amount of TRADENAME Cream applied with each treatment session will be documented. Laboratory parameters will be collected and patients will be monitored for photoallergic reactions.

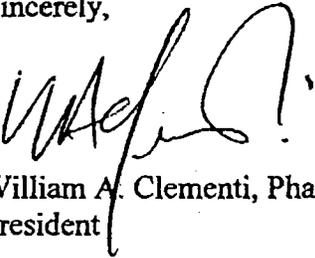
Jonathan Wilkin, MD, Director
July 21, 2004
Page 2.

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

A formal submission of the letter and 356H to NDA 21-415 will follow via Federal Express today.

If you have any questions, please do not hesitate to contact me.

Sincerely,



William A. Clementi, Pharm. D., F.C.P.
President

WAC/lee

CC: US and Norway Regulatory Files



CLEMENTI - KING
Global Regulatory Affairs

8 Tower Bridge
 Suite 1045
 161 Washington St.
 Conshohocken, PA 19428
 484-530-5110 - phone
 484-530-5120 - fax

Fax Cover Page

To:	Dr. Jonathan Wilkin	From:	Dr. William A. Clementi
Fax:	(301) 827-2091	Pages:	Including Cover - 3
Phone:	(301) 827-2020	Date:	July 21, 2004
Subject:	Phase 4 Commitments	cc:	

Comments

Dear Dr. Wilkin:

Attached is a copy of a letter being Federal Expressed to you today regarding Phase 4 Commitments.

Regards,

William A. Clementi, Pharm. D., F.C.P.

Notice: The documents accompanying this transmission contain confidential information that is legally privileged. This information is intended only for the use of the individual or entity named above.

If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or action taken in reliance on the contents of these documents is strictly prohibited. If you have received this information in error, please notify the sender immediately and arrange for the return or destruction of these documents.



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 20, 2004

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King for PhotoCure	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 3

Comments: Please find following the draft Phase 4 commitments. If these are acceptable please fax a letter stating that you agree to the Phase 4 commitments and list them. Also please send in a formal submission of the letter to the NDA.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Phase 4 Study Request Commitments

1. Conduct a systemic bioavailability study following application of methyl aminolevulinate cream with different concentrations ranging between 80 and 168 mg/g (preferably 80, 100, 120, 140 and 168 mg/g) in patients with multiple (8 – 10) actinic keratosis lesions. 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.

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

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.

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

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

/s/

Melinda Harris
7/20/04 02:18:10 PM
CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2004

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King for PhotoCure	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 2

Comments: Regarding your submission of December 16, 2003, requesting a re-review of the TRADENAME "Metvix", DMETS has reviewed your submission and the TRADENAME "Metvix" is not acceptable. Please let me know if you have any questions.

Document to be mailed: YES NO

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this page is the manifestation of the electronic signature.**

/s/

Melinda Harris
7/19/04 03:14:37 PM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)**

DATE RECEIVED: May 4, 2004

DUE DATE: June 5, 2002

ODS CONSULT #:

DATE OF DOCUMENT: December 16, 2003

PDUFA DATE: July 24, 2004

01-0218-4

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Melinda Harris, M.S.
Project Manager
HFD-540

PRODUCT NAME:
Metvix
(Methyl Aminolevulinate Cream) 168 mg/gram

NDA SPONSOR:
Clementi & Associates for PhotoCure ASA
Hoffsvveien 48
N-037 Oslo
Norway

NDA: 21-415

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

DMETS RECOMMENDATION:

PhotoCure has not provided persuasive evidence to diminish our concerns with potential confusion between Metvix and Mentax. Additionally, the independent analysis conducted by Med-E.R.R.S. concurred with DMETS' conclusion. Therefore, as noted in our previous review, DMETS does not recommend use of the proprietary name Metvix.

Carol Holquist, R.Ph..
Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REBUTTAL

DATE OF REVIEW: June 21, 2004

NDA # 21-415

NAME OF DRUG: Metvix (Methyl Aminolevulinate Cream) 168 mg/gram

NDA HOLDER: Clementi & Associates for PhotoCure ASA

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), to reconsider the acceptability of the proprietary name Metvix based on the sponsor's submission dated December 16, 2003. DMETS reviewed the proposed proprietary name Metvix in ODS consult # 01-0218-1, dated June 12, 2002. DMETS did not recommend use of the name, Metvix, due to the potential orthographic similarities to Mentax. The sponsor included an analysis, conducted by _____, on the trademark pair Metvix and Mentax. The sponsor did not submit revised container labels, carton labeling, and insert labeling for review and comment.

PRODUCT INFORMATION

"Metvix" cream contains the active ingredient methyl aminolevulinate. "Metvix" cream, in combination with red light illumination using the CureLight lamp, is indicated for the treatment of non-hyperkeratotic actinic keratoses. Topical application of methyl aminolevulinate results in formation of photoactive porphyrins, which are localized specifically in pre-malignant and malignant tumors of epithelial origin. When photoactive porphyrins are exposed to light of an appropriate wavelength in the presence of oxygen, a photochemical reaction takes place. This results in the production of singlet oxygen, which destroys intracellular components, in particular the mitochondria, leading to cell death. The activation of photosensitizers with resultant cytotoxicity forms the basis of photodynamic therapy of pre-malignant or malignant cells. Thus, application of "Metvix" cream to actinic (solar) keratoses causes photosensitization confined to the target lesions. Subsequent illumination of lesions leads to destruction of target lesions without risk to surrounding normal skin. Photodynamic therapy for actinic keratoses with "Metvix" cream is a two-stage process involving (1) superficial preparation of the lesions followed by application of "Metvix" cream to target lesions for 3 hours under occlusive dressing, and (2) removal of the dressing and rinsing off excess cream followed by illumination with red light of wavelength 570 to 670 nm and total light dose of 75J/cm², using a "CureLight lamp." "Metvix" cream is not intended for use with any device other than the CureLight lamp. "Metvix" cream will be available in 2-gram tubes containing 168 mg of methyl aminolevulinate per gram.

II. RISK ASSESSMENT:

The sponsor has requested a re-consideration of the proprietary name Metvix. The sponsor believes the risk of confusion with the trade name Mentax is minimal for the following reasons.

A. Trade Name Analysis Metvix and Mentax

PhotoCure states “there is only a moderate look-alike similarity (including in handwriting) and slight sound-alike similarity between the trademarks Metvix and Mentax.These assessments have been confirmed by a name-analysis between Metvix and the cited name Mentax performed by _____

DMETS RESPONSE: As noted in our previous review, both “Metvix” and Mentax begin with the letters ‘me’ and end with the letter ‘x’ and contain the same number of characters—six. Additionally, both products have the letter ‘t’ in the middle of the name. These similarities may contribute to misinterpretation of “Metvix” and Mentax prescriptions when scripted and upon verbal pronunciation. Additionally, “Metvix” and Mentax are both dermatological creams that will be applied topically which also increases the potential for confusion. DMETS notes that the _____ analysis also states the following. “...*This could create confusion with both a written or verbal medication order. Also the sound-alike similarity may be enhanced because both names contain two syllables and the first syllable sounds similar.*” It appears that _____ agrees that the potential for orthographic and phonetic similarity exists between Metvix and Mentax.

B. Metvix Cream is part of a process.

DMETS RESPONSE: DMETS acknowledges that Metvix cream is only to be used as a part of process that is conducted in physician offices or medical facilities. However, DMETS is concerned that patients may be written a prescription for Metvix with directions “as directed” and be instructed to return to the office/clinic with the drug. Thus the potential for misinterpretation of the proprietary name exists. _____ also noted “_____ believes that because of prescription drug reimbursement and health insurance issues, Metvix may be dispensed in an outpatient or retail pharmacy. We believe that patients may be sent to their local pharmacy with a prescription for Metvix with instructions to bring the “tube of cream” to the light treatment appointment. The directions on such a prescription may be vague or ambiguous (e.g., “as directed”). For example, some physicians give their patients prescriptions for Depo-Provera Injection or for Havrix Vaccine with the intent that the patient will fill the prescription at their local pharmacy, and then bring the vial of medication to the doctor’s office for administration.” Even though Metvix Cream is part of a treatment that is provided in a doctor’s office, this will not prevent the potential for confusion between Metvix and Mentax.

C. Metvix Cream is administered by a trained physician in the office.

DMETS RESPONSE: See II-B above.

D. Metvix Cream is supplied in 2 gram tubes.

DMETS RESPONSE: Although Metvix Cream is marketed in 2 gram tubes and Mentax Cream is marketed in 15 gram and 30 gram tubes, both products can be ordered as “#1, #2, etc” — also noted “*Although Metvix and Mentax have different percentage strengths, each comes only in one strength so the dosage strength may not be specified on a prescription order. As a result, both products may be prescribed as “dispense #1” (to indicate one tube)...*” Therefore, the different size tubes and the packaging of Metvix in a carton may not be sufficient to prevent the potential for confusion.

E. Metvix Cream requires special storage conditions.

DMETS RESPONSE: DMETS acknowledges that Metvix must be stored in a refrigerated environment whereas Mentax is stored at room temperature. This could help to decrease the potential for selection errors. However, differences in storage conditions do not always eliminate the risk of error. Post-marketing experience has demonstrated that errors occur between sound-alike and look-alike names despite the differences in physical characteristics or storage conditions. These differences may contribute to potential errors because practitioners may be more familiar with Mentax—a commonly used product—and therefore cognitively misinterpret a “Metvix” prescription for Mentax. Additionally, if the prescription has been cognitively misinterpreted, differences in physical characteristics or storage conditions would not prompt the practitioner that an error has occurred.

E. Metvix Cream will be prescribed to an elderly patient population.

DMETS RESPONSE: The age of the patient may not always be included on a written prescription. Both products are labeled for use in patients over the age of 18. A practitioner may only question the order if Metvix were prescribed for someone under the age of 18. Ages on the prescription would not prevent the practitioner from misinterpreting a Metvix prescription as Mentax (for a 65-year-old patient). Thus the age of the patient would not decrease the potential for name confusion between Metvix and Mentax.

F. — cited the following additional facts in their analysis of the potential for confusion between Metvix and Mentax.

- Both medications may be dispensed in an outpatient retail setting, in a hospital pharmacy that dispenses medications to a dermatology clinic and in an outpatient dermatology clinic,
- Both medications may be prescribed by the same type of physician (i.e., dermatologist),
- Each medication comes only in one strength so the dosage strength may not be specified on a prescription order,
- Both may cause burning, stinging, itching and erythema as potential adverse reactions, thus the adverse events may not prompt a patient to realize they have received the wrong medication

The — summary included the following statement:

— performed an internal failure mode and effects analysis comparing the trademarks Metvix and Mentax. Despite some clinical differences between the products, based on the — analysis, we believe that the trademarks Metvix and Mentax have the potential for confusion. We concur with the FDA DMETS review and agree that the trademark Metvix has the potential for creating confusion that could lead to medication errors.

In summary, the — analysis submitted by PhotoCure confirmed DMETS' concerns that there is a potential for name confusion between the two products Mentax and Metvix.

III. RECOMMENDATIONS:

PhotoCure has not provided persuasive evidence to diminish our concerns with potential confusion between Metvix and Mentax. Additionally, the independent analysis conducted by — concurred with DMETS' conclusion. Therefore, as noted in our previous review, DMETS does not recommend use of the proprietary name Metvix.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Denise P. Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
6/21/04 03:38:57 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/21/04 04:37:23 PM
DRUG SAFETY OFFICE REVIEWER



CLEMENTI-KING
Global Regulatory Affairs

8 Tower Bridge, Suite 1045
161 Washington Street
Conshohocken, PA 19428
regulatoryaffairs.com

VIA FEDERAL EXPRESS

June 10, 2004

Ms. Melinda Harris
FDA
Center for Drug Evaluation
Division of Dermatologic and Dental Drug
HFD-540
Rockville, MD 20850

RECEIVED

JUN 14 2004

MEGA / CDER

RE: Line Listings for Study PC T112/03 – 356h Serial #70

PRODUCT: PMA – P010061

SPONSOR: PhotoCure ASA, Oslo Norway, Clementi-King, Ltd. U.S. Agents

Dear Ms. Harris:

Per our conversation of June 7, 2004 enclosed, please find 1) Protocol with two Amendments (2), 2) Study Report 112-03 and 3) Line Listings.

If you have any questions, please do not hesitate to contact me.

Sincerely,

William A. Clementi, Pharm. D., F.C.P.
President

WAC/lee
Enclosures

CC: US and Norway Regulatory Files



CLEMENTI-KING

Global Regulatory Affairs

8 Tower Bridge, Suite 1045
161 Washington Street
Conshohocken, PA 19428
regulatoryaffairs.com

VIA FEDERAL EXPRESS

June 8, 2004

Ms. Melinda Harris
FDA
Center for Drug Evaluation
Division of Dermatologic and Dental Drug
HFD-540
Rockville, MD 20850

RECEIVED

JUN 09 2004

MEGA / CDER

RE: Line Listings for Study PC T112/03 – 356h Serial #69

PRODUCT: PMA – P010061

SPONSOR: PhotoCure ASA, Oslo Norway, Clementi-King, Ltd. U.S. Agents

Dear Ms. Harris:

Per our conversation of June 7, 2004 enclosed, please find the Protocol, Line Listing and Study Report 112-03 (Part I – Pages 1 – 24 plus signature pages and Part II – Pages 25 – 42 plus signature pages).

If you have any questions, please do not hesitate to contact me.

Sincerely,

William A. Clementi, Pharm. D., F.C.P.
President

WAC/lee
Enclosures

CC: US and Norway Regulatory Files



CLEMENTI-KING

Global Regulatory Affairs

8 Tower Bridge, Suite 1045
161 Washington Street
Conshohocken, PA 19428
regulatoryaffairs.com

VIA FED EXPRESS

Wednesday May 25, 2004

RECEIVED

JUN 02 2004

MEGA/CDER

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540
ODE V, CDER
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 29854

RE: Complete Response to NDA 21-415 (Type I Resubmission)

SPONSOR: PhotoCure ASA, Oslo Norway, Clementi-King, US Agents

Dear Dr. Wilkin:

Numerous conversations have taken place over the last two weeks between Melinda Harris, Mr. Felten, the reviewer for CureLight and me. Mr. Felten has assured me that all issues with CureLight (PMA # P-010061) have been addressed and the approval process is in the final stages.

During the telephone conversations, I received instructions from M. Harris and MJ K. Farnaro to submit the information listed below as a Complete Response to all outstanding issues to NDA 21-415. It is our understanding that this submission will be considered a Type I resubmission and pending satisfactory review, will be followed by an approval Action Letter. Contained in this Type I resubmission is the draft final labeling, a safety update and a restatement of our Phase IV commitments. These are detailed below.

1. Draft Final Labeling: The text of this labeling is identical to that agreed to with the Division in January 16, 2004.
2. A new Safety Update: The Safety Update includes all of the information requested in your letter of January 16, 2004. In accordance with your letter of January 16, 2004 the December 2, 2003 Safety Update is incorporated by reference to this Safety Update. One desk copy has been provided for ease of review. We also incorporate by reference our response to the Division's Request for Information dated December 8 and 11, 2003.

Please note that the cut-off date for this Safety Update is April 30, 2004. Only 4 serious adverse events (not related to MAL-PDT) and 1 non-serious event (labeled and related to MAL-

Jonathan Wilkin, MD, Director,
Division of Dermatologic and Dental Drug Products
Wednesday May 25, 2004
Page 2.

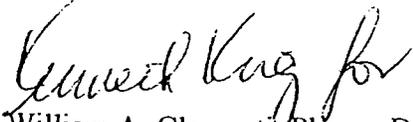
PDT) from post-marketing surveillance have been described herein (CRFs included). Also, we present data from one new completed Phase I study, PC T112/03. PhotoCure has reviewed the new safety information and believes that the safety data presented are consistent with previously submitted information and that no new safety concerns have arisen.

3. A commitment to perform the two Phase IV studies described below. These are scheduled to commence in July 2004, and enrollment targeted by the end of 2004. Each study will be completed 2 years later. Protocol development for these studies has already commenced and we look forward to receiving your input prior to study initiation.

- An in vivo biopharmaceutics study to assess the systemic bioavailability after application of methyl aminolevulinate cream of different concentrations in wide spread actinic keratosis. The protocol will be revised 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 cm^2 treated for each patient. Please note that this study will contain a description for methods to account for the amount drug applied to the patient by weighting tubes before and after application. This was an informational need asked for and responded to in December, 2003. The new information will provide more data on this topic.
- A 12 -month safety study in at least 200 evaluable patients with 10 or more actinic keratosis lesions with diameters of $\geq 4\text{mm}$, 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, will be included. Location of lesions will be sufficiently identified for long-term follow-up. The mass of TRADENAME Cream applied with each treatment sessions will be documented. Laboratory parameters will be collected and patients will be monitored for photoallergic skin reactions.

PhotoCure believes it has satisfied all outstanding issues related to the above referenced NDA and that there are no new safety issues which would delay approval of MAL-PDT.

Sincerely,



William A. Clementi, Pharm. D., F.C.P.
Managing Partner

WAC/lee

Cc: US and Norway Regulatory Files (2 file copies, 1 Desk copy, 1 Desk copy of Safety Update (2003))

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:

Melinda Harris, M.S.
Project Manager, DDDDP, HFD-540
CORP 2, N241

DATE April 28, 2004	IND NO.	NDA NO. 21-415	TYPE OF DOCUMENT Request for tradename, re-review	DATE OF DOCUMENT December 16, 2003
NAME OF DRUG METVIX		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE May 28, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
|--|--|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

The Sponsor is requesting that DMETS reconsider the use of METVIX as a name for methyl aminolevulinate hydrochloride cream. DMETS previously reviewed this name and found it unacceptable in a review dated June 12, 2002. The Sponsor has provided a summary for your review. This will be sent to you via courier.

SIGNATURE OF REQUESTER Melinda Harris, M.S.	METHOD OF DELIVERY (Check one) X <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Melinda Harris
4/28/04 02:58:39 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: May 25, 2004

To: Dr. William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King for PhotoCure	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 5

Comments: Minutes from the 5/10/04 tcon are provided

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 5/10/04, 10:00 A.M.

APPLICATION NUMBER: NDA 21-415

DRUG PRODUCT: TRADENAME (methyl aminolevulinate) Cream 16.8%

BETWEEN:

Name: William Clementi, Pharm.D., Managing Partner, Clementi-King
Kenneth King, Ph.D., Managing Partner, Clementi-King
K. Hestdal, M.D., Ph.D., Vice President of R&D
Kari Skinnenoen, Director of Regulatory Affairs

Phone: (484) 530-5110

Representing: PhotoCure ASA

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Mary Jean Kozma-Fornaro/ Chief, Project Management Staff
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-415

The teleconference was requested by the Sponsor to request specific information from the Agency concerning the resubmission of their NDA.

1. The Sponsor stated that they are ready to submit their Safety Update and asked the Agency what other issues or requests for information will there be that may delay the approval letter.

The Agency stated that the Sponsor should provide a Complete Response to the action letter dated January 16, 2004, which includes the agreed to labeling, the safety update and the agreement to the two Phase 4 commitments.

The Sponsor stated that they are providing suggested timelines in their response letter.

2. The Sponsor asked what they should provide in the safety update.

The Agency responded that the Sponsor should provide all relevant information that they have available.

3. The Sponsor asked the Agency what their cutoff date for the safety update should be.

The Agency responded that the Sponsor should decide on the cutoff date. Depending on what is submitted, the reviewer may request additional information.

4. The Sponsor asked what the timeline would be for obtaining final sign off.

The Agency stated that when the application comes in, the Division Director will determine whether the NDA is a Class 1 with a two month review period or a Class 2 with a six month review period. This application appears to be a Class 1 but if the safety update is extensive it could be a Class 2.

5. The Sponsor asked if there would be any additional Chemistry issues.

The Agency responded that the full team will review the resubmission and determine if there are additional issues.

6. The Sponsor asked about the process of approval with CDRH. They had spoken with Mr. Felten and were told that his review was complete and was waiting for sign off.

The Agency responded that they will be in contact with CDRH to determine the process.

The conversation ended amicably.

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this page is the manifestation of the electronic signature.**

/s/

Melinda Harris
5/24/04 11:02:30 AM
CSO

Mary Jean Kozma Fornaro
5/24/04 04:07:12 PM
CSO

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

/s/

Melinda Harris
5/25/04 02:24:10 PM
CSO



CLEMENTI KING
Global Regulatory Affairs

ORIGINAL

VIA FACSIMILE and FedEx

RECEIVED

JAN 26 2004

MEGA/CDER

January 23, 2004

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540
ODE V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20854

N-600(c)
NEW CORRESP

RE: NDA 21-415 Serial #67 – Letter to Mr. Felten re: PMA 010061/007

Dear Dr. Wilkin:

Attached please find a copy of a letter addressed to Mr. Richard Felten regarding the above referenced PMA. We've copied you on this letter so that simultaneous approval of each component of the combination product can be achieved with minimal delay.

Please let me know if you have any questions.

Sincerely,

William A. Clementi, Pharm.D., F.C.P.
Managing Partner
Clementi-King

Cc: US and Norway Regulatory Files, 356h Ser. #67



CLEMENTI KING
Global Regulatory Affairs

VIA FACSIMILE and FedEx

January 22, 2004

Mr. Richard Felten ✓
Director
Office of Device Evaluation (HFZ-410)
Division of General Restorative and Neurologic Devices
CDRH, Room 310K
9200 Corporate Blvd.
Rockville, MD 20850 ✓

RE: PMA 010061 Amendment 007

Dear Mr. Felten:

As per our discussion of January 16, 2004, we are providing you with the following information that satisfies all deficiencies mentioned by you. Dr. Wilkin in CDER, HFD 540 is also notified by way of this letter so that simultaneous approval of each component of the combination product can be achieved with the minimal amount of delay.

Briefly, this amendment contains the following: 1) information that harmonizes and cross references the device and drug label; 2) new design aspects for the control panel to prevent it from sliding have been provided; and, 3) prior responses concerning the protective sleeve for the horseshoe-positioning device are recapitulated herein.

We consider this amendment as addressing and, hopefully satisfying, all outstanding informational needs and requirements. If you need further information please call me so that we can expedite the final stages of approving TRADENAME PDT.

Sincerely,

William A. Clementi, Pharm.D., F.C.P.
Managing Partner
Clementi King

Cc: ✓ Dr. Jonathan Wilkin, CDER, HFD 540, FDA
US/Norway Regulatory Files



CLEMENTI KING
Global Regulatory Affairs

N 000(cc)

VIA FACSIMILE and FedEx

NEW CORRESP

January 22, 2004

RECEIVED

JAN 26 2004

MEGA/CDER

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540
ODE V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20854

RE: NDA 21-415, Response to Approvable Letter Dated January 17, 2004, Serial #66

Dear Dr. Wilkin:

PhotoCure ASA is in receipt of the above referenced letter. PhotoCure intends to keep NDA 21-415 "open" until a favorable action letter is received from you. PhotoCure understands that the approval of TRADENAME PDT relies on simultaneous "approval" of both the device and drug applications. Accordingly, it will have remedied the minor deficiencies in PMA 01006, as discussed with Mr. Felten.

Based on conversations held with Mary Jean Kozmo-Fanarro on January 21, 2004, we have agreed on final draft labeling (inclusive) and that only 2 Phase IV clinical requirements will be stated in the approval letter. These requirements are in accord with your meeting minutes issued on March 24, 2003.

We look forward to fast and prompt closure to the review process. PhotoCure will respond to all device issues by Monday, January 26, 2004.

Sincerely,

William A. Clementi, Pharm.D., F.C.P.
Managing Partner
Clementi-King

ORIGINAL

Cc: US and Norway Regulatory Files, 356h Ser. #66



CLEMENTI KING
Global Regulatory Affairs

ORIGINAL

VIA FACSIMILE AND FED EX

RECEIVED

January 16, 2004

JAN 20 2004

MEGA/CDER

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540,
Center for Drug Evaluation and Research ODE V
Food and Drug Administration
Rockville, MD 20854

N-000(BL)
ORIG AMENDMENT

RE: NDA 21-415 – Draft Labeling -- (Serial #65)

Dear Dr. Wilkin:

As a follow up to our phone conversation of January 15, 2004, please replace the following phrase, under Indications and Usage on page 4, with the phrase highlighted below.

“... lesion preparation (debridement using a sharp dermal curette) in the physician’s office when other therapies are unacceptable or considered less appropriate.”

Replace with: “...lesion preparation (debridement using a sharp dermal curette) in the physician’s office when other therapies are unsuitable or considered less appropriate.”

Additionally, please move the section entitled **Dermal Safety Studies**

The heading on page 7 should then be called
instead of ADVERSE REACTIONS.

Please call if you have any questions.

Sincerely,

William Clementi, Pharm D., F.C.P.
Clementi King Ltd.

Cc: US/Norway Regulatory Files 356h, Serial No. 65



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 16 January 2004

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King / <i>PhotoCure</i>	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 24

Comments: Action Letter is provided

Document to be mailed: YES NO

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CLEMENTI KING
Global Regulatory Affairs

VIA FACSIMILE AND FED EX

January 15, 2004

Jonathan Wilkin, MD
Director, Division Dermatologic and Dental Drug Products
HFD 540
ODE V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20854

RE: NDA 21-415 – Draft Labeling (Serial #64)

Dear Dr. Wilkin:

As a follow-up to our discussions of Jan. 14, 2004, we are providing you with the reference statement for the red light spectrum and drug interactions. This reference was in our annotated label submitted to you in our supplement of July 2003. It is contained in Vol. 1 page 27 or the last page of the annotated label.

We do not view this point a critical path issue at this time.

Sincerely,

William Clementi, Pharm D., F.C.P.
Clementi King Ltd.
161 Washington Street
8 Tower Bridge, Suite 1045
Conshohocken, PA 19428

RECEIVED

JAN 16 2004

MEGA/CDER

N-000(BL)

ORIG AMENDMENT

ORIGINAL

Cc: US/Norway Regulatory Files 356h, Serial No. 64



CLEMENTI KING

Global Regulatory Affairs

RECEIVED

JAN 16 2004

MEGA/CDER

REVISED

VIA FACSIMILE AND FED EX

January 14, 2004

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540,
Center for Drug Evaluation and Research ODE V
Food and Drug Administration
Rockville, MD 20854

N-000(BL)

ORIG AMENDMENT

RE: NDA 21-415 - Draft Labeling -- (Serial #63)

Dear Dr. Wilkin:

This letter is to confirm our telephone conversation of this date. Please insert the following phrase on line 168 "... /

Our discussions today were informative, and basically two words and one concept are in debate: "... /

Sincerely,


William Clementi, Pharm D., F.C.P.
Clementi King Ltd.

ORIGINAL

Cc: US/Norway Regulatory Files 356h, Serial No. 63



CLEMENTI KING
Global Regulatory Affairs

N-000(BL)

VIA FACSIMILE & Fed Ex

January 13, 2004

ORIG AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD 540
CDER, ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

RECEIVED
JAN 15 2004
MEGA/CDER

Re: NDA 21-415 Label Revisions

Dear Dr. Wilkin:

We are in receipt of draft label for the above referenced NDA. We propose to discuss the following changes in a TCON to be arranged for Jan. 14, 2004, morning:

1. Line 28: The sentence starting with 'contains in principle the same information as the previous sentence and is redundant. In addition, the Sponsor believes it has not provided evidence to support this more specific statement. Accordingly, this sentence should be deleted.
2. Line 118: The clinical studies that form the basis for the efficacy and safety of MAL PDT in treatment of patients with AK have all been performed in patients that could have other therapies. Thus the efficacy and safety of MAL PDT have been established in this patient population. Therefore, the following statement should be deleted from line 118 and 119 " —
3. Lines 132, 191 and 248: the word — should be deleted since this is an arbitrary descriptor without a reference standard. A bolded warning appears sufficient.
4. Lines 154-159: the information should be split into 2 sections: —
5. Lines 200-204: This topic was discussed at our pre-NDA conference and the point was made that photosensitizing for drugs occurs at a different wavelength (UV spectrum), which is lower than the red light spectrum.

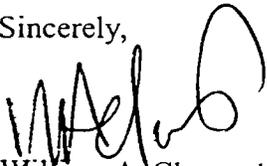
ORIGINAL

Published literature provides evidence in this regard. A statement reflecting this body of knowledge should be added to this section. We suggest

6. Sponsor cannot identify place for expiry dating on carton label.
7. Line 5 and Line 167 (terminology issue). Sponsor proposes that
8. Line 265. are noted supported by the listing in the table. The Sponsor suggests the use of
9. Line 333-335: Sponsor requests clarification on the limit of a half tube of cream per treatment session.
10. Line 172: Limits to two treatment sessions.
11. Line 256-259: Dermal Safety Studies: The Sponsor believes that the last sentence does not reflect the data and is inaccurate. Therefore this sentence should be deleted.
12. Line 285: The term implies that lesion differentiation to cancer occurs as a result of treatment. This inference, of course, is not correct and the sentence should be deleted.

We are requesting a TCON or procedural clarification on next steps for agreement and finalization of the draft labeling of Jan. 9, 2004. The Sponsor does not want to exceed the PDUFA date of Friday, Jan 16, 2004 for action letter response with final labeling accompanying that letter.

Sincerely,



William A. Clementi, Pharm.D.,F.C.P.
Managing Partner
Clementi-King Ltd.

CC Norway Regulatory Files, NDA 21-415 356h, Ser. #62



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 17 December 2003

To: Dr. William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi-King	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020

Subject: NDA 21-415

Total no. of pages including cover: 4

Comments: Minutes from the 12/4/03 tcon are provided

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 12/4/03, 11:00 A.M.

APPLICATION NUMBER: NDA 21-415

DRUG PRODUCT: Tradename (methyl aminolevulinate HCL) Cream, 16.8%

BETWEEN:

Name: William Clementi, Pharm.D., F.C.P., President
Phone: (484) 530-5110
Representing: Clementi and Associates

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jonathan Wilkin, M.D./Division Director
Stanka Kukich, M.D./Deputy Division Director
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology
Brenda Carr, M.D./Clinical Reviewer
Melinda Harris, M.S./Regulatory Project Manager

SUBJECT: NDA 21-415

The teleconference was requested by FDA to discuss specific information with the Sponsor concerning the submitted NDA.

1. The Agency stated that the Division is close to the end of the review cycle for the NDA and we have not received the safety update. The Division realizes that the safety update was requested late in the review cycle.

The Sponsor responded that the update was sent by FedEx on Tuesday. The Sponsor stated that if it would help the Division he could FedEx a desk copy immediately.

The Agency responded that it would be helpful to the reviewer to have the update as soon as possible.

The Sponsor stated that if the safety update does not contain sufficient information on specific patients, they could send out the Case Report Forms the same day.

2. The Agency stated that we are of the view that this product should only be dispensed to physicians.

The Sponsor responded that that is correct, the drug will only be dispensed to physicians.

The conversation ended amicably.

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/s/

Jonathan Wilkin
12/16/03 02:29:50 PM

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/s/

Melinda Harris
12/17/03 02:55:18 PM

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 16, 2003

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Melinda Harris, M.S., Regulatory Health Project Manager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for TRADENAME
(methyl aminolevulinate hydrochloride) Cream 16.8%,
NDA 21-415

Background

The sponsor revised and resubmitted Patient Labeling (PPI) to NDA 21-415 on November 21, 2003, based on our September 23, 2003, consult recommendations.

Comments

We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

We also have the following comments:

1. PPIs are intended to be read by patients prior to product use. It is still unclear whether or not the patient will receive this particular PPI prior to use of the product. TRADENAME (methyl aminolevulinate hydrochloride) Cream 16.8% will not be dispensed to patients directly, but instead will be used only in the offices of certain, qualified practitioners. The PPI will only serve as an effective communication or education tool for patients if practitioners are instructed to provide this leaflet to patients prior to their treatments with TRADENAME Cream.

2. Please add an Information for Patients subsection to the PRECAUTIONS section of the PI. This section should contain counseling information for the healthcare provider to provide to patients regarding the safe and effective use of the product. A PPI should not be a substitute for this section of the PI.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

4 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
12/16/03 01:55:12 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
12/16/03 04:28:17 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CLEMENTI
& Associates

ORIGINAL

VIA FACSIMILE and FEDEX

RECEIVED

DEC 18 2003

MEGA/CDER

Tuesday, December 16, 2003

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540
ODE V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20854

N-900(Bc)
ORIG AMENDMENT

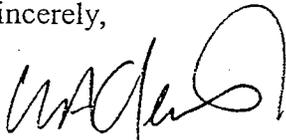
RE: NDA 21-415 TRADENAME for MAL PDT
Serial #61

Dear Dr. Wilkin:

PhotoCure is requesting that DMETS reconsider this use of Metvix for generic phrase MAL-PDT. Although the — reports shows similarity between Mentax (an antifungal) and Metvix, many other aspects how product use appear to distinguish the two names. These factors are explained in the attached summary. The — reports is provided in attachment (referred to as annex) in the summary.

PhotoCure is open to discussing this matter with you and hope to resolve this issue promptly.

Sincerely,



William A. Clementi, Pharm.D., F.C.P.

CC US and Norway Regulatory Files.

CLEMENTI
& Associates

VIA FACSIMILE AND FED EX

December 15, 2003

ORIGINAL

RECEIVED

DEC 17 2003

MEGA/CDER

Jonathan Wilkin MD
Director, Division Dermatologic and Dental Drug Products
HFD 540
ODE V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20854

RE: NDA 21-415, Serial # 60
Change of Name and Address for Clementi & Associates

N-000(XA)
ORIG AMENDMENT

Dear Dr. Wilkin:

Please be advised that Clementi & Associates recently had a name and address change. I've listed our new name and mailing address below for your reference. Please be sure that all records are changed to reflect this new information.

CLEMENTI KING LTD.
161 Washington Street
8 Tower Bridge, Suite 1045
Conshohocken, PA 19428
(484) 530-5110 - phone
(484) 530-5120 - fax

Sincerely,


William Clementi, Pharm D., F.C.P.
Clementi King Ltd.
161 Washington Street
8 Tower Bridge, Suite 1045
Conshohocken, PA 19428

Cc: US and Norway Regulatory Files



VIA FACSIMILE and Fed Ex

Friday, December 12, 2003

Jonathan Wilkin MD
Director,
Division of Dermatologic and Dental Drug Products
ODE V HFD 540
CDER
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

RE: NDA 21-415 Informational Needs: Biopharmaceutics

Dear Dr. Wilkin:

Reference is made to your request for information regarding PhotoCure's Phase I studies and the number of lesions per patient and the number of tubes used in those studies. Complete information about those topics is appended herein.

We are complying fully with your time specified for response by December 12, 2003.

Sincerely,

A handwritten signature in black ink, appearing to read "W. A. Clementi", written over a horizontal line.

William A. Clementi, Pharm.D., F.C.P.
US Agent PhotoCure ASA

CC: US and Norway Regulatory Files 356h Serial # 058



VIA FACSIMILE and Fed Ex

Friday, December 12, 2003

Jonathan Wilkin MD
Director.
Division of Dermatologic and Dental Drug Products
ODE V HFD 540
CDER
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

RE: NDA 21-415 Informational Needs: Clinical

Dear Dr. Wilkin:

Reference is made to your request for information regarding more medical information about adverse events occurring in the MAL-PDT post-marketing program. Requested information is provided herein. PhotoCure now considers the body of safety information complete—that is, no new data will be forthcoming.

We are complying fully with your time specified for response by December 12, 2003.

Sincerely,

A handwritten signature in black ink, appearing to read "W. A. Clementi", with a large, sweeping flourish at the end.

William A. Clementi, Pharm.D., F.C.P.
US Agent PhotoCure ASA

CC: US and Norway Regulatory Files 356h Serial # 059

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: ODS (Room 15B-08, PKLN Bldg.)		FROM: Melinda Harris, M.S. Project Manager, HFD-540 Division of Dermatologic and Dental Drug Products		
DATE December 9, 2003	IND NO.	NDA NO. 21-415	TYPE OF DOCUMENT Resubmission of NDA	DATE OF DOCUMENT July 17, 2003
NAME OF DRUG Tradename (methyl aminolevulinate hydrochloride) Cream, 16.8%	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE PDUFA due date: 1/17/04 Labeling Day #3 is 12/18/03
NAME OF FIRM: PhotoCure (US Agent: Clementi and Associates)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION <input type="checkbox"/> CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>This is a resubmission of the NDA following an Approvable letter. The Sponsor has revised the PPI per your request and it is attached.</p> <p>A labeling Day is scheduled for Thursday 12/18/03 at 1PM in Room N225 at CORP 2. Please provide comments by COB Tuesday 12/16.</p>				
SIGNATURE OF REQUESTER Melinda Harris, M.S. (301-827-2020)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

D

4 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Melinda Harris
12/9/03 09:42:01 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 8 December 2003

To: Dr. William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi & Associates	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 3

Comments: Clinical request for information. Please respond by Friday December 12, 2003.

Document to be mailed: YES NO

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NDA 21-415 Clinical Request for Information

Postmarketing Data Section 8.8 of PhotoCure's September 10, 2003 Dermatologic & Ophthalmic Drugs Advisory Committee Briefing Document contains ADR Reports (Section 8.8.5, pages 156 - 158). Where in the current Safety Update for NDA 21-415 (received December 3, 2003) are these postmarketing ADRs located? Of particular concern are the 2 cases of serious facial edema (DE-GD-0310425 and DE-GD-0310426) occurring in patients treated for actinic keratosis located on the scalp (Section 8.8.5.2, Serious and expected, page 157) in which one patient required hospitalization.

If these postmarketing ADRs are not included in the current safety update, please provide a safety update that includes data from all sources (e.g., post marketing, literature search) of the drug under consideration regardless of indication, dosage form, or dose level. Please describe in detail any significant changes of findings in the safety profile.

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/s/

Melinda Harris
12/8/03 03:26:27 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 8 December 2003

To: Dr. William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi & Associates	Division of Dermatologic & Dental Drug Products
Fax number: (484) 530-5120	Fax number: (301) 827-2091 or 2075
Phone number: (484) 530-5110	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 3

Comments: Biopharm request for information. Please respond by Friday December 12, 2003.

Document to be mailed: YES NO

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NDA 21-415 Biopharm Request for Information

In order to determine the dosing conditions that PK studies (101/97, 206/98 and 214/01) were conducted and to translate the information into appropriate labeling language, the sponsor is requested to provide the following information pertaining to each study:

1. Number of lesions treated on each patient.
2. Approximate surface area of each application site and the approximate total surface area of application of each patient.
3. Number of tubes used for each patient.
4. Number of grams used from each tube on each patient.

While bullets 1 and 2 will determine the total surface area involved, bullets 3 and 4 will give information on total amount of cream used. The four bullets as a whole will help to determine the average dose use and provide a general guide to clinical use.

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/s/

Melinda Harris
12/8/03 03:12:40 PM
CSO

MEMORANDUM OF TELECON

DATE: 12/4/03, 11:00 A.M.

APPLICATION NUMBER: NDA 21-415

DRUG PRODUCT: Tradename (methyl aminolevulinate HCL) Cream, 16.8%

BETWEEN:

Name: William Clementi, Pharm.D., F.C.P., President
Phone: (484) 530-5110
Representing: Clementi and Associates

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jonathan Wilkin, M.D./Division Director
Stanka Kukich, M.D./Deputy Division Director
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology
Brenda Carr, M.D./Clinical Reviewer
Melinda Harris, M.S./Regulatory Project Manager

SUBJECT: NDA 21-415

The teleconference was requested by FDA to discuss specific information with the Sponsor concerning the submitted NDA.

1. The Agency stated that the Division is close to the end of the review cycle for the NDA and we have not received the safety update. The Division realizes that the safety update was requested late in the review cycle.

The Sponsor responded that the update was sent by FedEx on Tuesday. The Sponsor stated that if it would help the Division he could FedEx a desk copy immediately.

The Agency responded that it would be helpful to the reviewer to have the update as soon as possible.

The Sponsor stated that if the safety update does not contain sufficient information on specific patients, they could send out the Case Report Forms the same day.

2. The Agency stated that we are of the view that this product should only be dispensed to physicians.

The Sponsor responded that that is correct, the drug will only be dispensed to physicians.

The conversation ended amicably.

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/s/

Jonathan Wilkin
12/16/03 02:29:50 PM



Via Fed-Ex

Tuesday, December 02, 2003

Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD 540
ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

RE: Safety Update NDA 21-415

Dear Dr. Wilkin:

Appended to this letter is all safety information for MAL-PDT. This information is current as of mid November, 2003 and is filed to the above referenced NDA at the request of the medical review officer. If you have additional questions please call me.

Sincerely,

A handwritten signature in black ink, appearing to read 'W. A. Clementi', written in a cursive style.

William A Clementi, Pharm.D.,F.C.P.
President Clementi & Associates, Ltd.

CC US and Norway Regulatory Files, 356h 048



VIA FACSIMILE & FEDERAL EXPRESS

Recode (N-000) BC
PER Pm
N-000 (BA) 11-28
ORIG AMENDMENT

Friday, November 21, 2003

Jonathan Wilkin MD
Director,
Division of Dermatologic and Dental Drug Products
HFD 540
ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

RECEIVED
NOV 24 2003
MEGA/CDER

**RE: Request for Informational Needs (Compliance with Re-write of PPI)
NDA 21-415**

Dear Dr. Wilkin:

Please find attached to this letter PhotoCure's response to informational needs due on November 20, 2003. Melissa Harris has been contacted by my office today and was informed that the package of materials will be sent Via Federal Express on Friday, November 21, 2003. Accordingly, we are complying fully with your request.

Of course, if questions arise, please do not hesitate to contact me.

Sincerely,

William A. Clementi, Pharm.D., F.C.P.
President
Clementi & Associates, Ltd.

DUPLICATE

Cc: US and Norway Regulatory Files

Enclosure: FDA form 356h



VIA FACSIMILE & FEDERAL EXPRESS

Friday, November 21, 2003

Jonathan Wilkin MD
Director
Division of Dermatologic and Dental Drug Products
HFD 540
ODE V
Food and Drug Administration
Rockville, MD 20854

RE: Informational Needs for NDA 21-415; Analytical Data Regarding Protective Gloves

Dear Dr. Wilkin:

Please find enclosed answers to your request for the above referenced NDA. We are complying with the specified time frame and believe we have provided a complete answer to the questions asked.

Sincerely,

A handwritten signature in black ink, appearing to read "W. A. Clementi", written over a large, stylized circular flourish.

William A. Clementi, Pharm.D., F.C.P.
President
Clementi & Associates, Ltd.

US Agent for PhotoCure ASA

Cc: US and Norway Regulatory Files

Enclosure: FDA form 356h (no desk copies)



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V**

FACSIMILE TRANSMITTAL SHEET

DATE: 21 November 2003

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi and Associates	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 2

Comments: Request for information. Please send to the Agency by Tuesday 11/25/03

Provide a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical, clinical studies, and other sources (e.g., post marketing, literature search) of the drug under consideration regardless of indication, dosage form, or dose level. Please describe in detail any significant changes of findings in the safety profile.

Document to be mailed: YES NO

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/s/

Melinda Harris
11/21/03 09:21:11 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 14 November 2003

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi and Associates	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 3

Comments: A CMC request for information is provided. Please respond by the end of next week.

Document to be mailed: YES NO

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NDA 21-415 Request for Information

In the 7/23/03 response to our Approvable letter, the response to our clinical issue 4A (“Identify types of gloves which methyl-ALA and excipients found in TRADENAME Cream will not penetrate”) appears in the clinical volumes, and references Appendix 5. Appendix 5 appears in volume 8, pp. 53-57. It includes only results, with minimal details of the testing procedure and analytical method used. Presumably the method is gas chromatography, since it is described as —

Please submit full details of the method used to test the gloves, along with similar information for the analytical method used to measure the amount of the drug product that permeated the glove. The submission should include chromatograms and a reference chromatogram showing the retention time for methyl-ALA under the conditions of analysis.

Please respond by the end of next week (11/21/03).

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/s/

Melinda Harris
11/14/03 11:20:03 AM
CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 14 November 2003

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi and Associates	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 3

Comments: A request for information is provided. Please respond by the end of next week.

Document to be mailed: YES NO

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 2020. Thank you.

NDA 21-415 Request for Information

The Division has received comments from the Office of Drug Safety regarding the Patient Package Insert. Please comply with the following:

1. Rewrite the PPI using a Medication Guide question and answer type format.
2. Simplify the language to a 6th to 8th grade reading comprehension level
3. Describe the process for patient and practitioner education.

Please respond by the end of next week (11/21/03).

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/s/

Melinda Harris
11/14/03 09:04:36 AM
CSO

e

5 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



VIA FACSIMILE and FEDERAL EXPRESS

Thursday, October 30, 2003

Jonathan Wilkin MD
Director,
Division of Dermatologic and Dental Drug Products
ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville MD 20854

RE:NDA 21-415 Informational Needs; Date Requested October 15, 2003

Dear Dr. Wilkin:

Please find appended to this letter, all informational needs requested on the above referenced date. I had called Melinda Harris one week ago and was granted slight extension to make this filing. I hope you find our answer complete and if you have further questions please contact me.

Sincerely,

W.A. Clementi / J.S.C.

WA Clementi Pharm.D., F.C.P.
US Agent PhotoCure AS

CC: Regulatory Files US Norway

1 Desk Copy to Melinda Harris

2 Submission Copies to NDA 21-415

1 Copy to Mr. Felten, CDRH

Enclosure: FDA 356h Form



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 15 October 2003

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi and Associates	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21415 request for information	

Total no. of pages including cover: 3

Comments: Clinical request for information

***Please respond no later than October 24, 2003

Document to be mailed: YES NO

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 received this document in error, please notify us immediately by telephone at (301) 827-
 2020. Thank you.

NDA 21-415 Request for Information

- 1) Study PC T 212/00
 - a) Please provide a listing of AEs for Table 36 Safety. Description of Adverse Events. Local adverse events. Safety/ITT population by treatment group (e.g., MAL-PDT vs. 20% ALA/Psoralein Cream).
 - b) (Vol. 9, pages 200 & 202) Why was the severity of pain listed as “moderate” and Listing 6 (pg. 202); however, the comment for Patient 19 (pg. 200) is as follows: “Severe pain during illumination”?
 - c) Please clarify why exanthema (listed as AE for Patient 29, Vol. 9, page 200, Listing 7) is not included in Listing 8, Vol. 9, pg. 202).
- 2) For Study PC T110/03, please provide the following:
 - a) Case Report Forms for Patients #15, 24, 36, 39, 68, 83, 135, & 146.
 - b) Where in the submission are the per subject erythema (irritation score) line listings located?
- 3) For Study PC T305/99, please provide Case Report Form for Patient 7009.
- 4) (Vol. 8 of 9, pg. 172, Attachment 8, Table 1) Please combine pruritus and itching and provide ITT population for patients reporting the event based on occurrence.
- 5) (Vol. 8 of 9, Pg. 183) Provide Case Report Forms for patients with “skin neoplasm malignant” listed as related.

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/s/

Melinda Harris
10/15/03 11:15:34 AM
CSO



VIA FACSIMILE/FEDERAL EXPRESS

Thursday, October 2, 2003

Melinda Harris
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation
HFD 540
Room# N241
9200 Corporate Blvd.
Rockville, MD 20850

**RE: NDA 21-415 Protocol and Related Documents, Informational Request
Deadline 10-5-03**

Dear Melinda:

Enclosed please find a CD-ROM labeled "Desk Copy" containing information regarding the above mention NDA. This completes your requested for information by facsimile dated September 30, 2003.

If you have any questions or comments, please call.

Sincerely,

A handwritten signature in black ink, appearing to read "W. A. Clementi", written over a horizontal line.

William A. Clementi, Pharm., D.F.C.P.
President
Clementi & Associates

Cc: PhotoCure, ASA

US and Norway Regulatory

Enclosures: CD-ROM; FDA 356H Form



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 30 September 2003

To: William Clementi	From: Melinda Harris, M.S. Project Manager
Company: Clementi and Associates	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21-415 AK indication Request for Information	

Total no. of pages including cover: 2

Comments: To ease the review, please provide the following information no later than Monday October 5, 2003

***An electronic copy of the following in Word sent to my attention as a desk copy: Clinical Response section in Volume 1.1, The response to the clinical questions found in the Clinical Section of the resubmission, and the Clinical Trial Report PC T110/03 including the protocol and amendments.

Document to be mailed: YES NO

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/s/

Melinda Harris
9/30/03 09:59:53 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 2003

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Melinda Harris, M.S., Regulatory Health Project Manager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for TRADENAME
(methyl aminolevulinate hydrochloride) Cream 16.8%,
NDA 21-415

Background

The sponsor resubmitted this NDA on July 17, 2003, following an Approvable Action. A draft Patient Package Insert (PPI) titled, "Information for Patients", has been submitted for review.

Comments

We have reviewed the PPI and have the following comments:

PPIs are intended to be read by patients prior to product use. It is unclear whether or not the patient will receive this particular PPI prior to use of the product. TRADENAME (methyl aminolevulinate hydrochloride) Cream 16.8% will not be dispensed to patients directly, but instead will be used only in the offices of certain, qualified practitioners. The PPI will only serve as an effective communication or education tool for patients if practitioners are instructed to provide this leaflet to patients prior to their treatments with TRADENAME Cream.

1. The PPI should be written in a Medication Guide question and answer type format as described in 21 CFR 208. Research and experience is available to support the communication effectiveness of the Medication Guide format. Alternate formats should have data (i.e., label comprehension studies) to support their communication effectiveness to a broad range of patients, including those with low literacy.

2. The wording in this PPI should be simplified in order to be understood a wider population of patients, especially those with low literacy. The PPI is written at a 10.1 reading comprehension level based on the Flesch-Kincaid Method. All patient materials should be written at a 6th to 8th grade reading comprehension level. 50% of the U.S. population reads below an 8th grade reading comprehension level.

3. In conclusion, we recommend that the sponsor:

- Rewrite the PPI using a Medication Guide question and answer type format
- Simplify the language to a 6th to 8th grade reading comprehension level
- Describe the process for patient and practitioner education

Please let us know if you have any questions.

give 5 days

comments

please

of from

comply w/

following

QOS

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/s/

Jeanine Best
9/25/03 08:22:55 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/25/03 01:47:58 PM
DRUG SAFETY OFFICE REVIEWER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-415	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: TRADENAME (methyl aminolevulinate) Cream, 16.8% in combination with the CureLight BroadBand Model CureLight 01		Applicant: Photocure ASA
RPM: Melinda Harris, M.S.		HFD-540 Phone # 301-827-2020
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
<input type="checkbox"/> Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<input type="checkbox"/> Chem class (NDAs only)		keratolytic
<input type="checkbox"/> Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		January 17, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<input type="checkbox"/> User Fee		<input type="checkbox"/> Paid
<input type="checkbox"/> User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<input type="checkbox"/> User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
<input type="checkbox"/> Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> Exception for review (Center Director's memo)		
<input type="checkbox"/> OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
<input type="checkbox"/> Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
<input type="checkbox"/> Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<input type="checkbox"/> For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
N/A	
General Information	
❖ Actions	
• Proposed action	() AP () TA (X) AE () NA
• Previous actions (specify type and date for each action taken)	AE September 19, 2002
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	January 16, 2004
• Most recent applicant-proposed labeling	November 21, 2003
• Original applicant-proposed labeling	July 17, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC December 30, 2003; November 10, 2003; September 25, 2003 DMETS October 8, 2003; June 12, 2002; January 2, 2002 DSRCS December 16, 2003; September 25, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	July 17, 2003
• Reviews	Yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	PIND/EOP2 June 22, 2000
• Pre-NDA meeting (indicate date)	May 2, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A

<ul style="list-style-type: none"> • Other 	N/A
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> • Date of Meeting 	N/A
<ul style="list-style-type: none"> • 48-hour alert 	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	N/A
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	January 16, 2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	July 23, 2002
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	January 16, 2004
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	January 16, 2004
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	October 24, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> • Clinical studies 	N/A
<ul style="list-style-type: none"> • Bioequivalence studies 	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	January 9, 2004
❖ Environmental Assessment	
<ul style="list-style-type: none"> • Categorical Exclusion <i>(indicate review date)</i> 	January 9, 2004
<ul style="list-style-type: none"> • Review & FONSI <i>(indicate date of review)</i> 	January 9, 2004
<ul style="list-style-type: none"> • Review & Environmental Impact Statement <i>(indicate date of each review)</i> 	January 9, 2004
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: July 25, 2002 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	October 1, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-415	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: TRADENAME (methyl aminolevulinate) Cream, 16.8%		Applicant: Photocure ASA
RPM: Voctoria Lutwak	HFD-540	Phone # 301-827-2020
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	keratolytic	
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates	September 26, 2002	
❖ Special programs (indicate all that apply)	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information		
• User Fee	<input type="checkbox"/> Paid	
• User Fee waiver	<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified	
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.	<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input type="checkbox"/> Verified	

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
General Information	
❖ Actions	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	September 27, 2001
• Original applicant-proposed labeling	September 27, 2001
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS June 12, 2002; January 2, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	September 27, 2001
• Reviews	Yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	PIND/EOP2 June 22, 2000
• Pre-NDA meeting (indicate date)	May 2, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	TL September 19 , 2002; September 17, 2002
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	September 12, 2002
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	July 23, 2002; May 9, 2002
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	September 12, 2002
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	June 5, 2002
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	July 19, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	July 29, 2002; July 24, 2002; July 1, 2002
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	July 1, 2002
• Review & FONSI (<i>indicate date of review</i>)	July 1, 2002
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	July 1, 2002
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	June 6, 2002
❖ Facilities inspection (provide EER report)	Date completed: July 25, 2002 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	August 4, 2002; July 21, 2002 (2)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: May 1, 2003
DOCUMENT DATE: Feb.12, 2003

DESIRED COMPLETION
DATE: September 20, 2003

ODS CONSULT #: 01-0218-2
01-0218-3

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Margo Owens
Project Manager
HFD-540

PRODUCT NAME:

Methyl Aminolevulinate Cream
16.8%

SPONSOR: PhotoCure ASA by
Penn Pharmaceutical Services

NDA #s 21-415 and 21-576

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the container label and carton and package insert labeling for methyl aminolevulinate cream 16.8%.

RECOMMENDATIONS:

DMETS recommends implementing the label and labeling revisions found in Section II of this review in order to minimize potential user error.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

PRE-MARKETING LABELING REVIEW

DATE OF REVIEW: September 15, 2003

NDA #s: 21-415 and 21-576

NAME OF DRUG: Methyl Aminolevulinate Cream
16.8%

NDA SPONSOR: PhotoCure ASA by
Penn Pharmaceutical Services

I. INTRODUCTION:

This consult is written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for a review of the container label, as well as the carton and package insert labeling for methyl aminolevulinate cream (NDA #s 21-415 and 21-576).

SUMMARY

The first proposed proprietary name for methyl aminolevulinate cream, Metvix, was submitted under NDA 21-415 (ODS Consult # 01-0218) for the indication of actinic keratosis. DMETS found Metvix acceptable in a review dated December 20, 2001. However, at the time of the initial review, the sponsor indicated that Metvix would not be dispensed in pharmacies, but would be distributed directly to healthcare practitioners. Based on this information, prescription study analysis studies were not conducted in the original review. The sponsor later stated that they were unsure of the distribution process for Metvix, and indicated that the product may be dispensed directly to patients from pharmacies. Consequently, DMETS re-reviewed the proprietary name, Metvix, on September 22, 2002, (ODS Consult # 01-0218-1), and did not recommend the use of the name due to its look-alike and/or sound-alike potential with other currently marketed products.

On February 21, 2003, the sponsor submitted a separate application (NDA 21-576), for methyl aminolevulinate cream, with an indication of basil cell carcinoma. The sponsor indicated that they would like to use the same tradename for both NDA 21-415 as well as NDA 21-576. Alternate proprietary names will be submitted at a later date. With the exception of the indication, the labeling for both products is the same. Once approved, the two application will be merged into a single application.

PRODUCT INFORMATION

Methyl aminolevulinate cream is an oil in water emulsion. When used in combination with red light illumination using the CureLight lamp, this product is indicated for the treatment of non-hyperkeratotic actinic keratosis (NDA 21-415) and basal cell carcinoma (NDA 21-576). Topical application of methyl aminolevulinate results in formation of photoactive porphyrins, which are localized specifically in pre-malignant and malignant tumors of epithelial origin. When photoactive porphyrins are exposed to light of an appropriate wavelength in the presence of oxygen, a photochemical reaction takes place. This results in the production of singlet oxygen, which destroys intracellular components, in particular the mitochondria, leading to cell death. The activation of photosensitizers with resultant cytotoxicity forms the basis of photodynamic therapy of pre-malignant or malignant cells. Thus, application of methyl aminolevulinate cream to actinic (solar) keratoses causes photosensitization confined to the target lesions. Subsequent illumination of lesions leads to destruction of target lesions without risk to surrounding normal skin.

II. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label, carton and package insert labeling for methyl aminolevulinate cream, DMETS has focused on safety issues relating to possible medication errors. We have identified areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Include the dosage form in the established name as follows:

TRADE NAME
(methyl aminolevulinate cream)
16.8%

2. Please ensure that the established name is at least ½ the size of the proprietary name, per 21 CFR 102.10(g)(2).
3. Include the route of administration per 21 CFR 201.100(b)(3).

B. CARTON LABELING

1. See comments under Container Label.
2. Relocate the route of administration to appear prominently on the main panel and revised to read "For topical use only".
3. We recommend including a statement "_____ " to minimize the risk that the product be used other than as intended.
4. We recommend relocating the storage condition statement to the primary display panel or bolding to prevent inadvertent storage at room temperature.
5. The statement "Use contents within one week after opening" should be relocated immediately after the statement "Duration for use: see enclosed package insert".

C. PACKAGE INSERT LABELING

1. See GENERAL COMMENT.
2. In the HOW SUPPLIED” section, please include a statement indicating the established name. For example, “Tradename cream contains 168 mg of methyl aminolevulinate per gram, and is supplied as follows.....”
3. Under “Product Package” please revise the statement — to read “For topical use only”.

III. RECOMMENDATIONS

DMETS recommends implementing the label and labeling revisions, as outlined in Section II of this review, in order to minimize potential error.

DMETS would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
10/8/03 02:48:31 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/8/03 04:24:15 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/8/03 04:39:54 PM
DRUG SAFETY OFFICE REVIEWER



From the CDER Electronic Document Room Staff

Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

To Contact: **William A Clementi** Fax: **610-581-7025** Phone: **610-581-7021**
Re: Firm: **Clementi** Application: [redacted] Letter Date: **7/24/03**

RESUBMISSION REQUIRED	
<input type="checkbox"/>	1. Document(s) submitted in non archival format (MS Word, etc.) – documents other than draft labeling text, should only be submitted in PDF format described in the guidance(s).
<input type="checkbox"/>	2. Labeling was submitted in MS Word format as described in the guidance, but without a corresponding PDF rendition - labeling should be submitted in PDF format. Draft labeling text may also be submitted in MS Word format, but all labeling submitted in word processing format should be accompanied in the submission by a PDF rendition.
<input type="checkbox"/>	3. Data set(s) submitted in non archival format(s) – SAS transport V5 as per SAS TS-140 (XPORT) is the format specified by the guidance.
<input checked="" type="checkbox"/>	4. Other - .JPG file formats are not accepted. Please follow guidance document and resubmit data to CDR.

RESUBMISSION NOT REQUIRED	
Your electronic records may have been delayed for the following reasons, but No further action is necessary at this time. Please address these issues in future submissions.	
<input checked="" type="checkbox"/>	1. Electronic Submission submitted to wrong address – If electronic components are included, submit entire submission (paper and electronic components) only to the CDR (see address above).
<input type="checkbox"/>	2. Duplicate copies of electronic media submitted - Submit only 1 set of electronic media, submitting a duplicate copy of electronic media may delay review and is unnecessary.
<input checked="" type="checkbox"/>	3. Electronic Table of Contents, e356h form and/or eCover Letter) not submitted - Including electronic PDF renditions of these paper documents, will help speed up the document room process.
<input checked="" type="checkbox"/>	4. Other – Insert electronic media only in archival copy and always send it to CDR.

For assistance or questions contact:
Office of Information Management – Ken Edmunds

Email (preferred) ESUB@CDER.FDA.GOV Phone: 301-827-7706

For Electronic Submission Guidance documents see:
<http://www.fda.gov/cder/regulatory/ersr/default.htm>

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REQUEST FOR CONSULTATION

TO (Division/Office):

Division of Drug Marketing, Advertising and
Communications, HFD-42
PKLN Room 17B04

FROM:

Melinda Harris, M.S.
Project Manager, HFD-540
Division of Dermatologic and Dental Drug Products

DATE 27 August 2003	IND NO.	NDA NO. 21-415	TYPE OF DOCUMENT Resubmission of NDA	DATE OF DOCUMENT July 17, 2003
NAME OF DRUG Tradename (methyl aminolevulinate hydrochloride) Cream, 16.8%		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE PDUFA due date: 1/17/04 Labeling will be mid November

NAME OF FIRM: PhotoCure ASA (US Agent: Clementi and Associates)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a resubmission of the NDA following an Approvable letter.

The Carton/Container label, Physician Insert and Patient Package Insert are attached. A hard copy will also be sent via courier.

A video was also included. Please look for and comment on promotional content in this instructional video. This video was included in the original NDA submission. This NDA is a drug-device combination. The device portion of the NDA is being reviewed in CDRH. The video is being sent via courier along with the consult.

A labeling Day will be scheduled for early to mid November of 2003. Please provide comments in a sufficient amount of time prior to the meeting. I will contact you when a day has been set up.

SIGNATURE OF REQUESTER Melinda Harris, MS, 7-2049	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Melinda Harris

8/28/03 10:10:26 AM

SIGNATURE OF REQUESTER Melinda Harris, M.S.	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Melinda Harris

8/27/03 03:05:47 PM



RECEIVED

AUG 20 2003

MEGA/CDER

VIA FEDERAL EXPRESS

N-000(BX) "C" per PM 8-25-03
ORIG AMENDMENT

Tuesday, August 19, 2003

Melinda Harris
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation
HFD 540
9200 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-415 AK Labeling

Dear Melinda:

Pursuant to our phone conversation, enclosed please find (2) CD-ROMS for the labeling discussions referencing the above-mention NDA.

If you have any questions or comments, please call.

Sincerely,

WA. Clementi, Pharm. D.F.C.P.
Clementi & Associates

Cc: PhotoCure, ASA

US and Norway Regulatory

Enclosure: FDA 356H; CD-ROMS

ORIGINAL

N-000-87C

CLEMENTI
& Associates

RECEIVED

JUL 25 2003

FDR/CDER ORIG AMENDMENT

VIA FEDERAL EXPRESS

RECEIVED

JUL 29 2003

Thursday, July 24, 2003

Randy Levin, M.D.
Lead Medical Officer
Food and Drug Administration
HFD-001 RM6A22
Rockville, MD 20857

CDR/CDER

RECEIVED

JUL 30 2003

MEGA/CDER

Re: NDA: 21-415 – Electronic Media Only (no paper copy)

Dear Dr. Levin:

Included with this letter is a CD-ROM containing the electronic form of data recently to the Division of Dermatologic and Dental Drugs Products for the NDA 21-415. This information represents a complete response to an Approvable letter. Would you please make this information available to the reviewing division.

Sincerely,



William A. Clementi, Pharm D.F.C.P.
President
Clementi & Associates

Cc: Kjetil Hestdal, PhotoCure, ASA

Enclosure: CD-ROM
FDA 356H Form

ORIGINAL



ORIGINAL

Federal Express

N-000(NC)
NEW CORRESP

Wednesday, July 23, 2003

Document Control Room
HFD-540
9201 Corporate Blvd.
Rockville, MD 20850

RECEIVED

JUL 24 2003

MEGA/CDER

RE: NDA 21-415

Dear Sir/Madame:

Enclosed please find copies of Page #33, which need to be inserted into all Volume #1, of the Complete Response Amendment to NDA 21-415, Serial #49. Please be advised, (6) copies of the above mention submission was Federal Express and received at your facility on Thursday, July 17, 2003.

Thank you for your assistance in this matter. If you have any questions, please contact me at (610) 581-7021.

Thank you,

A handwritten signature in black ink, appearing to read 'Judy Oswald'.

Judy Oswald
Office Manager
Clementi & Associates, Ltd.

WC:jdo

Encls: FDA Form 356h
(6) Copies page #33



CLEMENTI
 & Associates
FED EXPRESS

ORIGINAL

Wednesday, July 16, 2003

Jonathan Wilkin MD
 Director
 Division of Dental and Dermatologic Drug Products
 HFD-540, ODE V
 Food and Drug Administration
 9201 Corporate Blvd.
 Rockville, MD 20854

RECEIVED

JUL 17 2003

MEGA/CDER

**B2
 ORIG AMENDMENT**

RE: Complete Response Amendment to NDA 21-415

Dear Dr. Wilkin:

Reference is made to our "approvable letter" for the above referenced NDA. PhotoCure has conducted new clinical data to improve our understanding of contact sensitization and cross sensitization to endogenous aminolevulinic acid. This study complements data from yet another study, PCT 214/01 which clarifies the hazard of inadvertent exposure to the cream.

PhotoCure has sought the opinion of Dr. _____ who has reviewed our pre-clinical and clinical data regarding the effects of M-ALA on the liver. We believe that when the conservative criteria of 3x the upper limit of normal is applied to our data, this is no evidence of an hepatotoxic effect. In particular, there were no cases of frank hepatotoxicity in our clinical program.

A new instructional video has been developed and is provided herein. This video shows the safety precautions requested by the Division.

For issues related to labeling, we have identified where we agree and then when we feel our data support a more accurate conclusion, we propose new wording.

We believe this amendment well organized and will permit an efficient review. PhotoCure has noted "NEW" where new data has been presented or generated by new clinical studies (supra vide.) Other data has been re-analyzed to provide a comprehensive answer to the informational needs. We understand that a review time will be assigned to this amendment and we hope you will inform us of this date promptly.

Sincerely,

WA Clementi, Pharm. D.F.C.P.
 President, Clementi & Associates

Cc: Kjetil Hestdal, COO, PhotoCure, ASA

ORIG AMENDMENT

N-000/BC

CLEMENTI
& Associates

VIA FACSIMILE and FED EXPRESS

Friday, July 11, 2003

Jonathan Wilkin MD
Director
Division of Dental and Dermatologic Drug Products
HFD-540, ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20854

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JUL 14 2003

MEGA/CDER

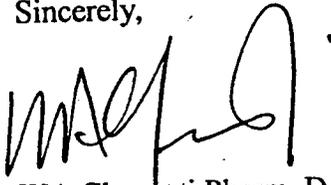
RE: NDA 21-415 and NDA 21-576

Dear Dr. Wilkin:

This submission provides new CMC information to the above pending NDAs for the Chemistry, Manufacturing and Controls section. We have provided proposals for changes in the specifications for the drug product to accommodate the change in the labeled amount of active ingredient from _____ to 168 mg/g _____

We also are providing an updated stability report that incorporates this change and proposes an expiry period. In addition we have modified the analytical method to improve the reproducibility and have included a report describing the proposed improvements and the associated method validation report.

Sincerely,



WA Clementi, Pharm. D.F.C.P.
President, Clementi & Associates

Cc: Kjetil Hestdal, COO, PhotoCure, ASA

Enclosure

ORIGINAL

CLEMENTI
& Associates

ORIGINAL

Fed EX

Friday, March 28, 2003

J. Wilkin MD
Director
Division of Dental and Dermatological Drug Products
HFD 540
ODE V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20852

RECEIVED
APR 01 2003
MEGA/CDER

NC
NEW CURTIS

RE: Meeting Minutes from Approvable Letter Meeting Dec. 16,2002 NDA 21-415

Dear Dr. Wilkin:

Attached herein is PhotoCure's version of the key points made at our above referenced meeting. We thank you for recently sharing your meeting minutes with us.

If you have any questions please call me.

Sincerely,



William A. Clementi, Pharm.D.F.C.P.
President, Clementi & Associates

Enclosure: Form FDA #356h; Meeting Minutes dated December 16, 2002.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 24 March 2003

To: William Clementi, Pharm.D.	From: Melinda Harris Project Manager
Company: Clementi and Associates for Photocure	Division of Dermatologic & Dental Drug Products
Fax number: (610) 581-7025	Fax number: (301) 827-2091 or 2075
Phone number: (610) 581-7021	Phone number: (301) 827-2020
Subject: NDA 21-415	

Total no. of pages including cover: 11

Comments: Minutes from the December 16, 2002 teleconference are provided

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

MEMORANDUM OF MEETING MINUTES



Meeting Date: December 16, 2002 **Time:** 10:00 AM
Location: N225 **Meeting ID:** 9648
Topic: NDA 21-415, TRADENAME Cream for actinic keratosis
Subject: Post-AE Discussion
Sponsor: Photocure ASA
Meeting Chair: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Meeting Recorder: Melinda Harris, M.S./Regulatory Project Manager, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
Brenda Vaughan, M.D./Clinical Reviewer, DDDDP, HFD-540
Paul Brown, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
Amy Nostrandt, Ph.D., D.V.M./Pharmacology Reviewer, DDDDP, HFD-540
Wilson DeCamp, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830
James Vidra, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
Shiowjen Lee, Ph.D./Biostatistcian, DBIII, HFD-725
Tapash Ghosh, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880
Richard Felten/Chemist, CDRH, ODE, DGRD, HFZ-410
Melinda Harris, M.S./Regulatory Project Manager, DDDDP, HFD-540

Sponsor Attendees:

Kjetil Hestdal, M.D., Ph.D./Vice President, Research and Development
Kari Skinnemoen, M.S./Director, Regulatory Affairs
Björg Bolstad, B.S./Clinical Trial Manager
Per Fuglerud, M.S./Statistician
William A. Clementi, Pharm.D., F.C.P./Regulatory Affairs, US Agent
Paul Clark/Vice President, Regulatory Affairs, Galderma

Purpose:

To provide general guidance on the content and format of the New Drug Application under 21CFR 314. The pre-meeting briefing document (submitted November 29, 2002) provides background and questions (pp 3-28) for discussion. The sponsor requests clarification on items contained in the approvable letter dated September 19, 2002.

Chemistry, Manufacturing and Controls:

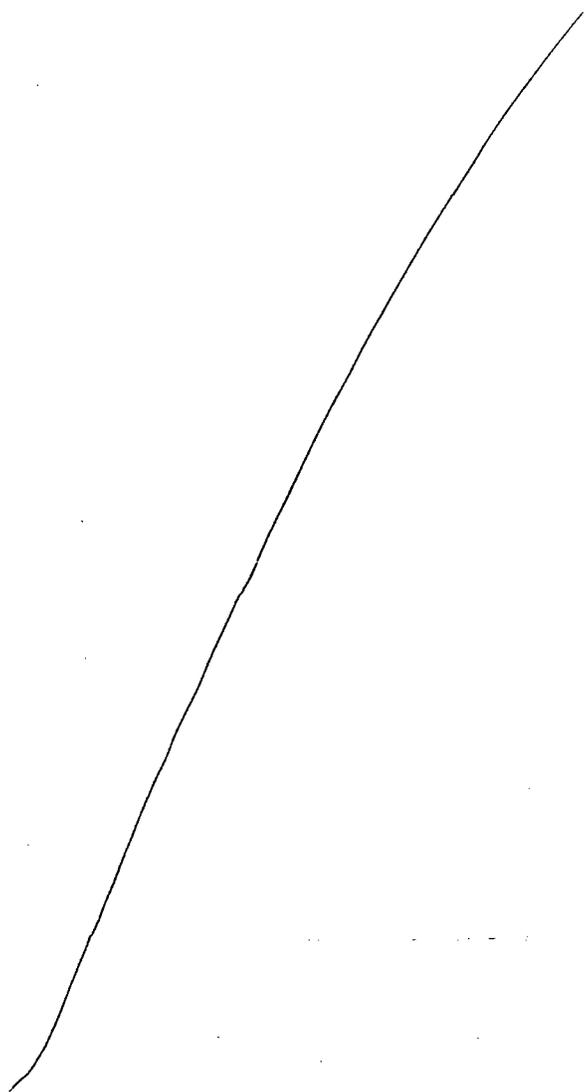
No CMC questions were identified in the briefing document. The Agency has the following comment in reference to the Clinical question 1.2:

Agency's Comment:

The determination of the maximum amount of the cream to be used at one time also has an impact on whether related substances (whether impurities or degradation products) will need to be identified for CMC or qualified for Pharm/Tox. Please refer to ICH Guidance Q3B ("Impurities in New Drug Products"), particularly Attachment 1, for additional details.

Pharmacology/Toxicology:

The Agency has the following comments regarding the sponsor's request to delete the
— from the — package insert: —



Biopharmaceutics:

Sponsor's Questions 1.2 and 1.3:

Photo Cure would like to discuss with FDA the need for a new bioavailability study. Should the FDA still require a new study, Photo Cure seeks further clarification on the requirements for study design and analytical method validation. If applicable, Photo Cure also would like to ask whether such a study could be performed as a Phase 4 commitment.

Photo Cure would like to discuss with the FDA the need for additional dose ranging and optimization of dosing.

Agency's Response:

Because of the interrelated nature of these questions, the following response addresses both issues.

While the Sponsor did conduct a number of in vivo biopharmaceutics studies as part of their 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. As for measuring penetration, one study was compromised in that the lesions were not "prepared" as is normally done prior to the application of the cream.

Application of the cream to "prepared" lesions could have a significantly better degree of penetration than what was originally seen in the Sponsor's NDA.

In terms of the types of studies we would like to see, the Agency would like to see the approved dose compared to lower doses in terms of both systemic availability and efficacy under the proposed conditions of clinical use. As the Sponsor was able to adequately assess both fluorescence and absorption in their previous work, a similar level of detail should be applied here. The sponsor is reminded to include a separate section under "Analytical Method Validation".

As for deferring the studies, they can be deferred to Phase 4.

Clinical:

Sponsor's Question 1.1.2 - Potential for Hepatotoxicity/Clinical Question 4C: Clinical studies (pages 9 of 62 -10 of 62):

The Sponsor proposes that the following be deleted from the PRECAUTIONS section of the label:

-

Agency's Response:

The Division recommends that the statement above be modified as follows:

Sponsor's Question 1.1.2 - Potential for Hepatotoxicity/Clinical Question 4C: Clinical studies (pages 9 of 62 -10 of 62):

The Sponsor proposes that the following be deleted from the INDICATIONS AND USAGE section of the label:

- "TRADENAME Cream (...) is indicated for treatment of non-hyperkeratotic actinic keratoses of the face and scalp

Agency's Response:

Submission and review of line listings for laboratory data (e.g., ALAT, ASAT, and bilirubin) obtained in patients with multiple lesions after a minimum of 2 TRADENAME Cream/PDT sessions (7 days apart) are needed prior to consideration of the Sponsor's proposed labeling modification and or deletions.

Sponsor's Question 1.2 - Request for New Bioavailability Study/Biopharm: Labeling (page 13 of 62):

The Sponsor proposes that the following be deleted from the DOSAGE AND ADMINISTRATION section of the label:

- "No more than 1 g (one tube) of product should be used for each
- "(...) using a total of 1 g of TRADENAME Cream."

Agency's Response:

The Division recommends the following clarification in the label:

Dosage and Administration

"No more than a total of 1-gram (1/2 of a tube) should be

The Division indicated that the 1 gram amount per treatment session was based on the maximum amount of study drug used in the Biopharm studies since the drug exposure data were not submitted to the NDA for the Phase 3 clinical trials. No data was presented on the number of tubes allotted per patient and total amount of drug applied per patient, although lesion data (size, location, and number) were tabulated. Instructions were to apply a layer of TRADENAME cream about 1 mm thick to the lesion and the surrounding 5 mm of normal skin. Drug (active and placebo) was supplied to study sites in 2-gram collapsible aluminum tubes. No known record of the number of tubes allotted or dispensed per patient was submitted to the NDA.

The Sponsor proposes that the following be deleted from the PRECAUTIONS – Information for patients section of the label:

-

Agency's Response:

The Division recommends the following clarification in the label:

Sponsor's Question 1.4 - Potential for Skin Sensitization (page 19 of 62):

PhotoCure is seeking clarification on the requirement for a 21-day contact sensitization potential study of methyl-ALA, especially with respect to the requirement to employ ALA-comparator (e.g., galenic formulation), in addition to methyl-ALA, in the challenge phase.

Agency's Response:

Unexpectedly, methyl-ALA has an unusually high contact sensitization potential; therefore, cross sensitization with endogenous ALA is a concern with use of the product by the patient and staff administering the drug product.

Question 1.5 - Barrier Method for Prevention of Cross-Contamination with the CureLight 01 Device/Clinical Question 4S (page 21 of 62):

The Sponsor proposes adjusted text in the Package Insert under DOSAGE AND ADMINISTRATION, Step 5 of the procedure (Illumination of TRADENAME Treated lesion).

Agency's Response:

The sponsor will need to describe these in terms of material, biocompatibility and light transmission for the sleeve covering the calibration probe. The use of clear sleeves is acceptable as a means of preventing contamination. The Sponsor will need to describe how they are placed and/or attached to the calibration probe and positioning device. The Agency will need data on spectrum transmission and energy transmission through the sleeve to insure that this does not alter treatment dosing.

Sponsor's Question 1.6.1 - Phase 4 Commitments/Clinical Question 6 (page 22 of 62):

The Sponsor is willing to conduct a clinical — study in patients with multiple AK lesions located on the face and scalp to document the effect of multiple treatments and recurrence rates, but proposes changes to the proposal from the FDA:

Agency's Response:

As one of the conditions of approval, a commitment to conduct a — safety study in patients with multiple (5–10) AK lesions located on the face and scalp in 100 to 200 patients to document the effect of multiple treatments and recurrence rates is needed. Clinical laboratory data from patients with multiple lesions (≥ 4 lesions) treated at least twice (7-days apart) with TRADENAME indicating a lack of clinically relevant findings in Phase 2 or Phase 3 clinical trials were not submitted to the NDA; therefore, hepatic transaminases (ALAT and ASAT), alkaline phosphatase, total bilirubin, and CBC should be obtained. Inclusion of patients of Asian and Hispanic heritage is recommended.

Question to the Sponsor:

(page 22 of 62): Under study design, what is meant by the use of "fractionated" TRADENAME Cream PDT treatment in the re-treatment and recurrence study?

Additional Comments:

- A strategy for patients who have many lesions, perhaps staggering the application of the cream to various lesions to insure that no lesion is treated outside the time window of 3½ hours should be included.
- The Sponsor should collect data regarding total illumination time per patient, the number of lamps used, and the number of treatment fields per patient.
- Safety of treating overlapping treatment fields should be addressed.
- The Sponsor should include methods to avoid cross-contamination between patients with use of the device in the protocol and user manual.
- The Sponsor should collect adverse events separately to assess drug effect alone from PDT for each of four time periods (AEs resulting from the curettage procedure, during drug application, illumination, and post-treatment) as to the type and quantity of the adverse event.
- The use of anesthetics/analgesics should be documented.
- An investigator “licensed to practice medicine” in the locale in which the study is conducted should be in charge of monitoring local and systemic safety.

Sponsor’s Question 1.6.1 Clinical Question 6C - Question for discussion (page 24 of 62):

PhotoCure proposes to apply for a waiver for a photoallergenicity study.

Agency’s Response:

A clinical dermal safety study to determine the photoallergenicity potential of TRADENAME Cream with a diluted form of TRADENAME Cream conducted as a Phase 4 study is needed. The Division recommends that the Sponsor use low doses of material with a solar simulator light source with cut-off filters that allows screening out the upper UVA/blue wavelengths in some sites and use full UVA and/or visible at others to distinguish protoporphyrin stimulation effects versus possible allergic effects.

Sponsor’s Question 1.7 — (page 24 of 62):
/

Agency’s Response:

Efficacy data from the cryotherapy arm of the studies submitted with the NDA were not be used to support approval. /

Sponsor’s Question 1.8 - Effect of Lesion Preparation (debridement procedure) (pages 27-28 of 62):

The Sponsor proposes to replace the term — with “debridement” throughout the package insert.

For example:

The Sponsor proposes that the text of the INDICATION AND USAGE section be modified as follows:

Agency's Response:

The Division recommends the following:

“TRADENAME Cream in combination with 570 to 670 nm wavelength red light illumination using the CureLight BroadBand Model CureLight 01 lamp is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp in _____ when used

— in conjunction with lesion preparation

Other Issues

Sponsor's Question 2.4.3 Clinical Question 3 - Visual instructional Material (page 31 of 62):

The Sponsor is proposing to reach agreement with the Division on the final written labeling before the final development of the visual aid.

Agency's Response:

Concurrence on the final written label prior to final development of the visual aid is an acceptable approach; however as the visual aid is an integral part of the label for this drug product, final label approval is dependent upon both written and an acceptable visual aid.

Biostatistics:

No Statistics issues were identified in the briefing document.

Additional Administrative Comments:

1. The Sponsor is encouraged to provide specific questions and briefing materials for meeting requests based on specific informational needs.

Action Items:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. Biopharm Phase 4 Question	Biopharm Reviewer	

NDA 21-415 12/16/02 meeting

Minutes Preparer: _____
Melinda Harris, M.S./Regulatory Project Manager, DDDDP, HFD-540

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP, 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/

John Kelsey
3/24/03 02:16:48 PM
for Dr. Wilkin

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

/s/

Melinda Harris
3/24/03 02:29:03 PM
CSO

(7)

2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

CONTACT INFORMATION

NAME OF APPLICANT Cure ASA	DATE OF SUBMISSION February 5, 2003
PHONE NO. (Include Area Code) 581-7021	FACSIMILE (FAX) Number (Include Area Code) (610) 581-7025
CONTACT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, S. License number if previously issued): Cure ASA veien 48 77 Oslo way	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Clementi & Associates, Ltd. Suite 214, Building 3 919 Conestoga Road Rosemont, PA 19010

PRODUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 21-415		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) yl aminolevulinate hydrochloride	PROPRIETARY NAME (trade name) IF ANY Metvix [®] Cream	
MEDICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) N/A	CODE NAME (if any) P-1202	
DRUG FORM: Cream	STRENGTHS: 168 mg/g	ROUTE OF ADMINISTRATION: Topical
PROPOSED INDICATION(S) FOR USE: s		

APPLICATION INFORMATION

APPLICATION TYPE (check one)		
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF ANDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Holder of Approved Application		
TYPE OF SUBMISSION (check one)		
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER
IF SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION First follow up to Letter off January 21, 2003		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		

NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
-----------------------------	---

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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FEB 13 2003

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3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

C

January 27, 2003

C **MENTI**
Associates
VIA FEDEX

Document Control Room
FDA
9201 Corporate Boulevard
Rockville, MD 20850

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JAN 28 2003
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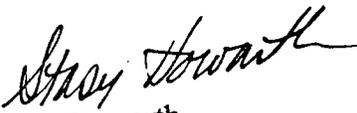
NDA 21-415, Sponsor PhotoCure, Metvix Cream for Actinic Keratosis

To whom it may concern:

I am enclosing an original and two copies of the above referenced document.
Please forward a copy to:

Jonathan Wilkin M.D.
Director, Division of Dermatologic and
Dental Drug Products (HFD 540)
Food and Drug Administration
9201 Corporate Blvd
Rockville, MD 20854

Thank you,



Stasy Howarth
Office Manager
Clementi & Associates Ltd.

WAC: sh
Enclosures

ORIGINAL

CLEMENTI
& Associates

APPEARS THIS WAY
ON ORIGINAL

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JAN 28 2003
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CSIMILE and FedEx

January 21, 2003

Dr. Wilkin, M.D.

Director of Dermatologic and Dental Drug Products

U.S. Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20854

Re: NDA 141-415, Sponsor PhotoCure, Metvix Cream for Actinic Keratosis

Dear Dr. Wilkin:

Enclosed are an original and two copies of the above referenced document. I regard the proposals in the enclosed letter as interesting and valid approaches to improve our efficiencies in drug development.

If you have any questions, please don't hesitate to call.

A copy of this letter was faxed to Melinda Harris on January 22, 2003. She suggested the original be filed to the referenced NDA.

Sincerely,



William A. Clementi Pharm.D., F.C.P.

President
Clementi & Associates Ltd.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved. OMB No. 0910-0188
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
MegaCure ASA

DATE OF SUBMISSION
January 21, 2003

TELEPHONE NO. (Include Area Code)
(477) 581-7021

FACSIMILE (FAX) Number (Include Area Code)
(610) 581-7025

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
U.S. License number if previously issued):
MegaCure ASA
Korsveien 48
N-0377 Oslo
Norway

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
Clementi & Associates, Ltd.
Suite 214, Building 3
919 Conestoga Road
Rosemont, PA. 19010

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-415

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Methyl aminolevulinat hydrochloride

PROPRIETARY NAME (trade name) IF ANY
Metvix[®] Cream

CODE NAME (if any)
P-1202

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) N/A

DRUG FORM: Cream

STRENGTHS: 168 mg/9

ROUTE OF ADMINISTRATION: Topical

PROPOSED INDICATION(S) FOR USE: Actinic Keratosis

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

LABELING SUPPLEMENT

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

AS SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION Letter January 21, 2003

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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JAN 28 2003

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PAGE 1

FORM FDA 356h (4/00)

APPEARS THIS WAY
ON ORIGINAL

November 29, 2002

Via Fed Ex

Jonathan Wilkin M.D.
Director, Division of Dermatological and
Dental Drug Products (HFD 540)
Food and Drug Administration
9201 Corporate Blvd
Rockville, MD

RECEIVED
DEC 02 2002
MEGA/CDER
mk
ORIG AMENDMENT

RE: Response to Action Letter; NDA 21-415, Metvix Cream in Actinic Keratosis, PhotoCure
ASA; Briefing Document for Meeting on December 16, 2002 10:00 AM.

Dear Dr. Wilkin:

PhotoCure has enclosed a document being a combined Briefing Document for the Meeting on
December 16, 2002 and responses to the points made in your action letter dated September,
2002. For purposes of expediting the meeting, PhotoCure has divided the Briefing Document
into two parts:

- Section 1.1 to 1.8 presents the issues the sponsor wants to be discussed at the meeting
- Section 2.1 to 2.5 assumes a structure that uses all points outlined in the action letter and
present the sponsors proposed responses.

For each section appropriate background information is provided in marked attachments.

PhotoCure attendees include: Kjetil Hestdal M.D., Ph.D., Kari Skinnemoen M.S., Bjørg Bolstad
B.S., Per Fuglerud M.S., William A. Clementi Pharm.D., F.C.P. (US Agent) and Paul Clark,
Regulatory Affairs, Galderma (a new marketing partner). We request the attendance of Mr.
Richard Felten to resolve outstanding issues with the PMA.

Finally, we understand that we will be receiving the Division's comments a few days before the meeting. PhotoCure will be at the Latham Hotel in Georgetown beginning on Saturday 14, 2002 (Latham Phone Number: 202.726.5000). You may also reach me on my cell at 610.952.1234.

We look forward to meeting with you.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates

US Agent

WAC: sh

Enclosures

Cc: US and Norway Regulatory Files

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT PhotoCure ASA	DATE OF SUBMISSION October 25, 2002
TELEPHONE NO. (Include Area Code) (610) 581-7021	FACSIMILE (FAX) Number (Include Area Code) (610) 581-7025
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): PhotoCure ASA Hoffsveien 48 N-0377 Oslo Norway	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Clementi & Associates, Ltd. Suite 214, Building 3 919 Conestoga Road Rosemont, PA 19010

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-415		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) methyl aminolevulinate hydrochloride	PROPRIETARY NAME (trade name) IF ANY Metvix Cream	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A	CODE NAME (If any) P-1202	
DOSAGE FORM: Cream	STRENGTHS: 168 mg/g	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: Actinic Keratosis		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Confirmation of Meeting to Discuss Information Needs and Data Requests Described in Approvable Letter (Dated September 19, 2002)
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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Associates

DUPLICATE

RECEIVED
NOV 08 2002
MEGA/CDER

VIA FACSIMILE

nc
NEW CORRESP

Wednesday, October 16, 2002

Sandy Childs
Attention: Dr. Wilkin and V. Lutwak
HFD-580
Office of Drug Evaluation 5
9201 Corporate Blvd.
Rockville, MD 20854

RE: Confirmation of Meeting to Discuss Informational Needs and Data Requests Described in Approvable Letter (Dated September 19, 2002)

NDA 21-415, Sponsor PhotoCure, Metvix Cream for Actinic Keratosis

Dear Ms. Childs,

I'm writing to confirm our meeting on December 16th, 2002 at 10:00AM. We will provide suitable background documents (12 desk copies and one archival copy) by December 2nd. As discussed with Ms. Lutwak if the background documents are ready before that time we will, of course, submit them. We plan no changes to the attendee list and look forward to meeting you again in December.

Of course, if an earlier date should arise in your busy schedule, please allow us the opportunity to have the meeting sooner than December 16th.

Sincerely,

William A. Clementi Pharm.D., F.C.P.
President
Clementi & Associates Ltd.

WAC: sh
CC: Norway and US Regulatory Files



DUPLICATE RECEIVED

NOV 08 2002

MEGA/CDER

VIA FACSIMILE

Monday, October 14, 2002

Sandy Childs
Attention: Dr. Wilkin and V. Lutwak
Division of Dermatological and Dental Drug Products
HFD-580
Office of Drug Evaluation 5
Food and Drug Administration
9201 Corporate Blvd.
Rockville MD 20854

**RE: Request for Meeting to Discuss Informational Needs and Data Requests
Described in Approvable Letter (Dated September 19, 2002)**

NDA 21-415, Sponsor PhotoCure, Metvix Cream for Actinic Keratosis

Dear Ms Childs:

Pursuant to an action letter issued by the Division on the above referenced date, PhotoCure is requesting a meeting to discuss topics outlined in the approvable letter referenced above. Dr. Wilkin suggested that we should review the letter and then, when we felt ready to "come in", discuss any points of concern with the reviewing group. PhotoCure now accepts this invitation.

Specifically, six members of PhotoCure will attend the meeting: Kjetil Hestdal MD, Kari Skinnemoen MS., Per Fuglerud MS, Bjorg Bolstad BS, Paul M. Clark (Galderma-marketing licensee) and of course, William A. Clementi, Pharm.D., F.C.P. We are asking for a courtesy which will be our request to hold one open position for the meeting in the event an immuno-dermatologist can attend.

We understand that this meeting may not include labeling discussions. Accordingly, PhotoCure wishes to focus on the following points addressed and elaborated on in the approvable letter:

1. Clarification of the requirement to conduct a 21 day dermal sensitization study.
2. Clarification to satisfy the Biopharmaceutics information needs
3. Clarification regarding the barrier methods to resolve safety concerns about the use of the horseshoe-positioning device.

4. Discussion of the validity of an apparent "signal" in the form of elevated liver transaminases in pre-clinical studies.
5. The use of lesion preparation in the placebo and treatment groups in Study PC T306/99.
6. Clarification of any and all Phase IV commitments.

PhotoCure will submit a "Briefing Document" 14 days before the meeting (12 copies marked as desk copies, and one copy to NDA 21-415). The format of the Briefing Document will parallel closely the outline of points made in the approvable letter.

PhotoCure is requesting a meeting as soon as possible and is available the last week of October or early November.

Your cooperation is greatly appreciated.

Sincerely,



William A. Clementi Pharm.D., F.C.P.
President
Clementi & Associates Ltd.

WAC:sh

Cc: Norway and US Regulatory Files

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION</p> <p>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE</p> <p><i>(Title 21, Code of Federal Regulations, 314 & 601)</i></p>	<p><i>Form Approved: OMB No. 0910-0338</i> <i>Expiration Date: March 31, 2003</i> <i>See OMB Statement on page 2.</i></p> <p style="text-align: center;">FOR FDA USE ONLY</p> <p>APPLICATION NUMBER</p>
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APPLICANT INFORMATION	
<p>NAME OF APPLICANT PhotoCure ASA</p>	<p>DATE OF SUBMISSION September 27, 2002</p>
<p>TELEPHONE NO. (Include Area Code) (610) 581-7021</p>	<p>FACSIMILE (FAX) Number (Include Area Code) (610) 581-7025</p>
<p>APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): PhotoCure ASA Hoffsveien 48 N-0377 Oslo Norway</p>	<p>AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Clementi & Associates, Ltd. Suite 214, Building 3 919 Conestoga Road Rosemont, PA 19010</p>

PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-415		
<p>ESTABLISHED NAME (e.g., Proper name, USP/USAN name) methyl aminolevulinate hydrochloride</p>	<p>PROPRIETARY NAME (trade name) IF ANY Metvix Cream</p>	
<p>CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A</p>	<p>CODE NAME (If any) P-1202</p>	
DOSAGE FORM: Cream	STRENGTHS: 168 mg/g	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: Actinic Keratosis		

APPLICATION INFORMATION	
<p>APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)</p>	
<p>IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)</p>	
<p>IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Holder of Approved Application</p>	
<p>TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER</p>	
<p>IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____</p>	
<p>IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)</p>	
<p>REASON FOR SUBMISSION Notification of Intent to Amend</p>	

<p>PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)</p>	
<p>NUMBER OF VOLUMES SUBMITTED</p>	<p>THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC</p>
<p>ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/Testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.</p>	

<p>Cross References (list related License Applications, INDs, NDAs, PMAs, 610(k)s, IDEs, BMFs, and DMFs referenced in the current application)</p>
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This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306(k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to Action Letter

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 810, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Stuart H. Smith, Jr. William A. Clementi</i>	TYPED NAME AND TITLE William A. Clementi, Pharm.D. F.C.P. President, Clementi & Associates Ltd	DATE September 27, 2002
ADDRESS (Street, City, State, and ZIP Code) Suite 214, Building 3, 919 Conestoga Road, Rosemont, PA 19010		TELEPHONE NUMBER (610) 581-7021

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



VIA FACSIMILE AND FEDEX

September 27, 2002

Ms. Victoria Lutwak
FDA
Office of Drug Evaluation V
Center for Drug Evaluation & Research
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: Notification of Intent to Amend
NDA 21-415 - Metvix (methyl aminolevulinate) Cream

Dear Ms. Lutwak:

I am forwarding Form FDA 356h, "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" together with a copy of a letter addressed to Dr. Jonathan K. Wilkin on behalf of William A. Clementi Pharm.D., F.C.P. and PhotoCure.

Please advise us if you have any questions or require additional information.

Thank you,

A handwritten signature in cursive script, appearing to read "Stasy Howarth".

Stasy Howarth
Office Manager

WAC: sh
Enclosures



VIA FACSIMILE and Fed-Ex and Email (V. Lutwak)

Thursday, September 26, 2002

Jonathan K Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
ODE V
CDER
Food and Drug Administration (FDA)
9201 Corporate Blvd
Rockville, MD 20854

RE: Action Letter of Approvability of NDA 21-415, Metvix (methyl aminolevulinate) Cream,
Sponsor PhotoCure ASA

Dear Dr. Wilkin:

Reference is made to 21 CFR 314.110 in which PhotoCure notifies the FDA of the Sponsor's intention to file an amendment to the above referenced NDA, and by so doing, complies with the mandate of notification so stipulated in the above referenced title. Pursuant to 21 CFR 314.102, PhotoCure is requesting a meeting to discuss the further steps needed before the application can be approved.

Because PhotoCure believes it can resolve most of the issues required for approval in a timely manner, we believe the meeting between the Division and Sponsor should take place as soon as possible.

I will call Ms. Lutwak to obtain procedural information about the meeting.

This letter confirms our intentions which were verbally communication to the Division on September 25, 2002.

Sincerely,

A handwritten signature in black ink, appearing to read "W.A. Clementi", with a large, sweeping flourish at the end.

William A. Clementi Pharm.D., F.C.P.
President
Clementi & Associates Ltd.
US Agent, PhotoCure ASA

cc: Regulatory Files US and Norway

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 20, 2002
TO: NDA 21-415
FROM: Victoria Lutwak, Project Manager, HFD-540
SUBJECT: Confirmation of receipt of action letter faxed on
September 20, 2002

Dr. Wilkin called, at the appointed time, to inform Dr. Clementi that we took an action on the application. The NDA is approvable with the deficiencies listed in the letter along with information request in draft labeling. The Agency will at Dr. Clementi's request discuss what further steps need to be taken before the application may be approved. We will fax a copy of the letter to him immediately and he will be mailed the official copy. We requested that Dr. Clementi confirm that the transmission was complete which he did.

From the AE letter 09-19-02:
Tel 610-581-7021
Photocure ASA
Attention: William A. Clementi, Pharm.D.
919 Conestoga Road
Rosemont, PA 19010

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....

cc:
Archival IND/NDA 21-415
HFD-540/Div. Files
Drafted by: vl/09-29-02
Initialed by: vl

MEMORANDUM

10 DFS
9/20/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
MegaCure ASA

DATE OF SUBMISSION
August 9, 2002

PHONE NO. (Include Area Code)
(610) 581-7021

FACSIMILE (FAX) Number (Include Area Code)
(610) 581-7025

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
U.S. License number if previously issued):

MegaCure ASA
Korsveien 48
0377 Oslo
Norway

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
Clementi & Associates, Ltd.
Suite 214, Building 3
919 Conestoga Road
Rosemont, PA 19010

PRODUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-415

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
MINOLEVULINIC ACID

PROPRIETARY NAME (trade name) IF ANY
Metvix[®] Cream

GENERIC/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A

CODE NAME (If any)
P-1202

DOSE FORM: Cream

STRENGTHS: 168 mg/g

ROUTE OF ADMINISTRATION: Topical

PROPOSED INDICATION(S) FOR USE: Actinic Keratoses

CLASSIFICATION INFORMATION

APPLICATION TYPE

- (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION

RESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT

LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Clarification and general correspondence

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
List the locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name,
address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing)
conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

REFERENCES (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED

AUG 12 2002

MEGA/CDER

APPEARS THIS WAY
ON ORIGINAL

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& Associates

RECEIVED

AUG 12 2002

MEGA/CDER

VIA FACSIMILE and Fed EX

Thursday, August 08, 2002

ORIGINAL

Dr. J. Wilkin MD
Director,
Division of Dermatological and Dental Drug Products (HFD 540)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE:NDA 21-415, Metvix[®] Cream

NC

NEW CORRESP

Sponsor: PhotoCure ASA

Dear Dr. Wilkin:

Upon reflection on comments made during our July 26, 2002 TCON, I would presume that some or part of the following points may help resolve the open reviews. We are not providing new data but trying to clarify elements of the application that may be confusing. For example, contact hypersensitivity is a safety point that requires some elaboration. The study conducted by (PC T108/01) shows two levels of severity; mild and moderate. Three out of 25 subjects had mild to moderate scores in the challenge phase and at re-testing, so skin sensitization can not be ruled out. The point estimate for the incidence is 3/25; i.e. 12%, with a exact two-sided 95% confidence interval of (2.5% - 31%), and the upper limit of the exact one-sided 95% confidence interval is 28% (Armitage and Berry: *Statistical Methods in Medical Research*, second edition, p 115-120, 1997).

PhotoCure understands that complete disclosure of this information is appropriate in the product label. A point of note however is that the results in this study did not predict the clinical trial experience. Repeat light exposure to the same area has been performed in the Basal Cell Carcinoma program, where patients received repeat treatment at three months. The above referenced NDA contains such data (Item 8H - Integrated Summary of Safety). In these studies comprising 370 patients, there is one report of mild hypersensitivity skin related to treatment (study PC T205/98). This patient reported mild hypersensitivity at visit 1, meaning that the hypersensitivity could not be due to previous exposure to Metvix, but could be due to possible hypersensitivity to the one or more of the ingredients.

RECEIVED
AUG 1 2 2002
MEGA/CDER

VIA FACSIMILE and Fed EX

Monday, August 05, 2002

ORIGINAL

Dr. J. Wilkin MD
Director,
Division of Dermatological and Dental Drug Products (HFD 540)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD

RE:NDA 21-415, Metvix[®] Cream

NEW CORRESP

Sponsor: PhotoCure ASA

Dear Dr. Wilkin:

On behalf of PhotoCure, I am writing to confirm discussion I had Ms. Lutwak, who kindly responded to my letter of July 28, 2002. During her call of August 1, 2002 she confirmed that my letter of July 28, 2002 had accurately captured the main points of our July 26, 2002 TCON, in which PhotoCure was informed that an action letter could not sent at that time because of open reviews.

We further discussed that the Division will be issuing an action letter in August. We briefly discussed the two remaining options : 1) an approvable letter containing information requests and deficiencies that may involve Phase IV commitments, or 2) a disapproval letter outlining deficiencies. Both actions allow PhotoCure to have a hearing and meet with the Division. Also either action will be preceded by a telephone call from you. It my understanding that in the event of a disapproval letter, PhotoCure does not have to withdraw the above referenced NDA but can choose to amend the NDA with new data that may satisfy the Divisions concerns.

I believe the above statements accurately reflect our very informative conversation. Please note that during the week of August 19, 2002 I will be out of the country but that my staff in the office can locate me if required.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates Ltd.

July 30, 2002

Via Facsimile and Fed-Ex

RECEIVED
AUG 12 2002
MEGA/CDER

ORIGINAL

J. Wilkin M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD 540)
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD

NC
NEW CORRESP

RE: NDA 21-415, Telephone Conference (TCON) July 26, 2002

Dear Dr. Wilkin:

In response to the above referenced TCON PhotoCure wishes to share the following comments:

As stated during the call, "faulty telephone or speakerphone connection" occurred and accordingly PhotoCure wishes to verify that all issues described during the call are accurate and complete. A partial summation is provided:

- a. The Division's review is not yet complete and will not complete in the 10 month PDUFA first target date (Friday July 26, 2002). The review of NDA 21-415 cannot be completed because of possible unresolved issues (*infra vide*, c.), and because the scope of answers that PhotoCure provided in response to the Division's informational requests was apparently insufficient.
- b. The Division will complete its review in the next the two months but an "approval" letter will not be issued. It is possible that an approvable letter with certain conditions or a disapproval letter will be issued by the 12 month PDUFA target date (September 27, 2002).
- c. The Division expressed its concern in the following areas: contact hypersensitivity (*infra vide*, d.), PpIX fluorescence, and use of lesion preparation procedures described in the Phase III studies and application of those procedures intended for physician's instruction for use of Metvix PDT.
- d. Reference was made to a contact hypersensitivity "signal" from one or more of the Phase I studies conducted under

PhotoCure ASA requests confirmation that these are all the items mentioned by you as possible reasons for the anticipated regulatory action.

Because of understandable time constraints, PhotoCure did not have a chance to clarify these points raised by the Division during this most recent TCON. In general, TCONs of the past several weeks were informative in that the Division instructed PhotoCure of the Division's assessment and possible future regulatory action(s), but PhotoCure has not had the opportunity (within the time or format of the TCON) to clarify points of concerns or express its views.

PhotoCure has sought to maintain clear communication with the Division throughout the drug development and dossier review process, and wishes to continue working in this manner. Further, PhotoCure believes it has answered all the Division's informational requests in a timely and appropriate manner. **Now, PhotoCure is concerned because it does not understand the basis for all new issues raised in the TCON.** It is difficult for PhotoCure to understand, for example, what is meant by a "signal of contact hypersensitivity" (point d. supra vide). Accordingly, PhotoCure is requesting the possibility to discuss these issues before the issuance of a regulatory disposition letter, in a meeting or in a TCON. We believe a strong scientific exchange can be effective and benefit both the Sponsor and the Division. Pursuant to CFR 314.125, draft labeling is an important part of the approval/disapproval decision. PhotoCure is fully willing to discuss any revisions and/or additions to the proposed draft labeling which the Division deems appropriate, as well as any commitments in connection with unresolved issues as deemed appropriate by the Division. Please advise accordingly.

PhotoCure believes we can resolve the Divisions concerns by dialogue and more in-depth explanation of data already contained in NDA 21-415, and will discuss any commitments the Division deems appropriate.

We hope you will honor our request.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates Ltd

CC: Regulatory Files US and Norway



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 7-23-02 ²⁴

To: William Clementi, Pharm.D.	From: Victoria Lutwak
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415 PLEASE NOTE THE ADDITION OF #13 An additional new request for information.	

Total no. of pages including cover: ~~2~~ 3

Document to be mailed: YES NO

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Please note the addition of a
 new item: #13 —

Vickey

Informational needs:

During conduct of the Phase 3 studies:

- 1) Was there any patient discomfort associated with lesion preparation?
- 2) Did the investigators use anesthetics prior to lesion preparation?
- 3) Did or should investigators use gloves during Metvix cream application?
- 4) Are there any personnel protection instructions for inadvertent exposure to Metvix cream?
- 5) Is Tegaderm® transparent or translucent, and what instructions were given to patients regarding restrictions during the 3-hour interval between Metvix application and removal?
- 6) Did patients experience any AEs (e.g., burning, stinging, itching, etc.) during Metvix application prior to removal? If so, what was the remedy?
- 7) What instructions were provided regarding use of 2 lamps? Was there a strategy developed for cream removal, avoidance of overlapping treatment fields, etc.? Should there be a limit to the number and location of treatment fields?
- 8) 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 Metvix cream?
- 9) Since the Sponsor did not provide disinfection/sterilization procedures, what techniques were employed by the investigators for between patient use of the device?
- 10) Did the study nurse follow a triage protocol for referral to the sub-investigator for treatment of local adverse events?
- 11) Who recorded local and systemic AEs at the following:
 - a) before and after each treatment session,
 - b) at 2 week post-treatment visit, and
 - c) 3-month efficacy endpoint visit?
- 12) Were there post-treatment instructions provided for patients (e.g., restrictions immediately after treatment, remedies for possible AEs such as swelling, burning, crusting, etc.).
- 13) Please describe how Metvix cream was applied during the Phase 3 studies. The Dosage and Administration section of the draft label indicates that Metvix should be applied using a spatula.

NDA 21-415

July 24, 20002

- 13) Please describe how Metvix cream was applied during the Phase 3 studies. The Dosage and Administration section of the draft label indicates that Metvix should be applied using a spatula.

**APPEARS THIS WAY
ON ORIGINAL**



NDA ORIG AMENDMENT

Bm

July 24, 2002

VIA FACSIMILE and FEDEX

RECEIVED
JUL 26 2002
MEGA/CDER

Jonathan Wilkin M.D.
Director,
Division of Dental and Dermatological Drug Products (HFD 540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-415 - Informational Requests (Numbers 1-13) on July 23 and 24, 2002

Dear Dr. Wilkin:

PhotoCure ASA has attached detailed responses to the Division's informational responses requested from the company yesterday. Within the limits of the data collected (i.e. timing of adverse events relative to cream application), PhotoCure believes it has answered the question in a satisfactory manner. Also, and as with all clinical studies, some investigating centers employed procedures unique to their practice situation like the use of different disinfecting agents. (See attached).

If you or members of the reviewing staff have any questions please do not hesitate to contact me.

Sincerely,

William A. Clementi, Pharm.D. F.C.P.
President
Clementi & Associates Ltd

CC: Regulatory Files US and Norway
FDA Form 356h (No: 40)

Desk Copy to Ms. Victoria Lutwak via Facsimile

ORIGINAL



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5.

FACSIMILE TRANSMITTAL SHEET

DATE: 7-23-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>V.L.</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	<i>Please - ASAP!</i>

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Informational needs:

During conduct of the Phase 3 studies:

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- 2) Did the investigators use anesthetics prior to lesion preparation?
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- 9) Since the Sponsor did not provide disinfection/sterilization procedures, what techniques were employed by the investigators for between patient use of the device?
- 10) Did the study nurse follow a triage protocol for referral to the sub-investigator for treatment of local adverse events?
- 11) Who recorded local and systemic AEs at the following:
 - a) before and after each treatment session,
 - b) at 2 week post-treatment visit, and
 - c) 3-month efficacy endpoint visit?
- 12) Were there post-treatment instructions provided for patients (e.g., restrictions immediately after treatment, remedies for possible AEs such as swelling, burning, crusting, etc.).



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 7-23-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject: Re: TRADENAME
Your request for information for NDA 21-415 dated July 18, 2002

Total no. of pages including cover: ~~2~~ 3

COMMENTS TO THE SPONSOR:

The Division of Medication Errors and Technical Support does not recommend the use of the proprietary name Metvix. The primary concern is related to a name that already exists in the US marketplace, Mentax. DMETS' previous assessment of Metvix and Mentax noted that there were similarities but the risk of Metvix and Mentax being used in error was reduced due to the controlled supervised setting in which Metvix will be used. This conclusion was based on the fact that Metvix would only be distributed to trained healthcare practitioners and would not be available via prescription. DMETS re-assessed the potential name confusion between Metvix and Mentax based on the possibility that Metvix will be distributed via prescription.

Both "Metvix" and Mentax begin with the letters 'me' and end with the letter 'x' and contain the same number of characters—six. Additionally, both products have the letter 't' in the middle of the name. These similarities may contribute to misinterpretation of "Metvix" and Mentax prescriptions when scripted and upon verbal pronunciation. "Metvix" and Mentax are both dermatological creams that will be applied topically. Although the dosing intervals differ between "Metvix" and Mentax, topical creams are often written with 'use as directed' instructions. Physicians may write 'use as directed' on "Metvix" prescriptions because they have counseled patients about returning to the office with the medication. Although "Metvix" is available as a 2 gram tube and Mentax as 15 and 30 gram tubes, the dispensing quantity may be written as '#1' in lieu of the actual packaging quantity. These additional similarities increase the risk that these products may have a higher potential for confusion.

"Metvix" will be stored in the refrigerator and probably will not be routinely dispensed in pharmacies. One would think that this would help to reduce the potential for medication errors between "Metvix" and Mentax. However, differences in storage conditions do not always eliminate the risk of error. Postmarketing experience has demonstrated that errors occur between sound-alike and look-alike names despite the differences in physical characteristics or storage conditions. These differences may contribute to potential errors because practitioners may be more familiar with Mentax—a commonly used product—and therefore cognitively misinterpret a "Metvix" prescription for Mentax. Additionally, if the prescription has been cognitively misinterpreted, differences in physical characteristics or storage conditions would not prompt the practitioner that an error has occurred. Moreover, name confusion or cognitive errors between "Metvix" and Mentax may also occur during the restocking of pharmacy or nursing storage bins. This type of error could result in decreased "Metvix" potency, since approximately 10% of "Metvix's" efficacy is lost if stored at room temperature for more than three months.

Document to be mailed:

YES

NO

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ORIGINAL

NEW CORRESPONDENCE
NC

CLEMENTI
& Associates

July 18, 2002

Jonathan Wilkin M.D.
Director
Division of Dental and Dermatological Drug Products (HFD 540)
Center for Drug Evaluation and Research)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RECEIVED
JUL 22 2002
MEGA/CDER

RE: NDA 21-415 Request for Additional Trade Names

Dear Dr. Wilkin:

Reference is made to our TCON of June 26, 2002 in which a request was made by you for PhotoCure ASA to submit 3 additional trade names to the Division. We understand that the proposed trade name Metvix[®] has been reviewed by the Office of Medication Errors. PhotoCure ASA has undertaken a search for new trade names, but this process, the legalities notwithstanding, is lengthy and time consuming and requires the company to conduct market research on name recognition parameters in the dermatology healthcare sector. We are requesting that the concerns over the existing name be shared with PhotoCure ASA so that the company can understand if there is concern over similarities in the prefix and annunciation likeness or if a specific marketed product was found in conflict with the name Metvix. Our search of name databases did not reveal an obvious conflict but our search may not have been conducted in the same manner as the Office of Medication Errors.

We hope you will honor our request and share your findings regarding naming conflicts with us so that we can expedite the resolution of your request. If you have any additional questions please call me at (610) 581-7021.

Sincerely,



William A. Clementi, Pharm.D. F.C.P.
President
Clementi & Associates Ltd

CC: Regulatory Files US and Norway
FDA Form 356h (No: 39)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak



RECEIVED

June 28, 2002

VIA FACSIMILE & FEDEX

JUL 0 5 2002

MEGA/CDER

ORIGINAL

Jonathan Wilkin M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

NC
NEW CORRESP

RE: Response to June 26, 2002 TCON (NDA 21-415)

Dear Dr. Wilkin:

Enclosed is a clarification request for questions presented by facsimile to PhotoCure on June 26th, 2002. Clarification of the Division's questions is important in order to provide satisfactory answers to the Division in a timely way. PhotoCure welcomes the opportunity to have a brief TCON to discuss the points described in the attached "Request for Clarification".

Furthermore, PhotoCure is requesting the opportunity to bring the light device into the Division sometime in July 2002 and demonstrate to you and the medical reviewing staff the full and complete operation of the device. It is apparent from Question 1, that there may be some misunderstanding on how the device and dose calibration is used with a patient. Please let us know if a demonstration is possible. We believe that a demonstration would clarify many issues associated with efficacy and transmission of diseases.

We look forward to your prompt response.

Sincerely,

William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 38)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

June 27, 2002

VIA FACSIMILE & FEDEX

ORIGINAL

Jonathan Wilkin M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

RECEIVED
JUN 28 2002
MEGA/CDER

RE: Response to June 26, 2002 TCON (NDA 21-415)

NEW CORRESP

Dear Dr. Wilkin:

PhotoCure ASA is responding to a Question that was asked during a June 25th FDA/Clementi & Associates Ltd telephone contact with Ms. Victoria Lutwak. Ms. Lutwak asked about the marketing of Metvix[®] Cream in other countries and post-marketing adverse events (AEs).

Metvix[®] Cream has been approved for sale in both Sweden and Norway. Post-marketing adverse events are reported to the MPA (Swedish Health Authorities) then the MPA forwards the reports to PhotoCure ASA. The same procedure applies to Norway. To date, no AE's from these countries have been reported to PhotoCure ASA.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 37)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 6-25-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	

Total no. of pages including cover: 3

Comments: Please see following pages. If you have any question, please call me.

It is important that we get this information in a timely manner, please estimate when

we can expect a response to this request. Thank you.

Document to be mailed: YES NO

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NDA 21-415 Metvix-PDT

Informational Request

1. The Sponsor has proposed use of _____



We are recommending that a clear covering be used on the diode _____ Use of an appropriate disposable cover is also recommended for the horseshoe-positioning device, since the placement of this device on intact epidermis cannot be guaranteed in patients with multiple AKs that have been prepared for therapy.

If the Sponsor agrees with the suggestion to use a clear covering to insure non-transfer of infectious material, the Sponsor will need to address the following:

- Demonstrate that the material does not significantly alter light transmittance. This can be done by making measurements using the calibration probe with and without the covering material over the light receptor. The difference in transmission should be easily detected by this method.
- Use animal models to test with the covering material in place for representative lengths of time relevant to clinical use to see if it produces a heat problem that results in formation of a moisture barrier.
- Provide a revised operator manual clearly specifying dosimetry/calibration and treatment with such a barrier in place.
- Discuss/ address the issue of treating multiple AK's in terms of side by side lesions and how to prevent light field overlapping if the lesions are close to each other but can not be treated in a single field.
- Provide a discussion regarding the horseshoe shaped position device in terms of what its intended use is. Is this for determining distance to insure correct spot size or does it have some function regarding centering of lesion? Is the device designed so that it has an acceptable excess of area to allow sufficient normal skin remaining around the lesion? Provide the diameter of the horseshoe shape opening.
- How the light measuring probe is used (e.g., held by the user during calibration or simply lay on the site).

2. The repeated dose minipig study was requested at the End-of-Phase 2 meeting to support the Sponsor's Phase 3 clinical trials; however, the report for that study was submitted for the first time with the NDA. A possible liver toxicity signal was

detected in the repeated dose data in the minipig study(e.g., slight increase in ALT) ; therefore, systemic laboratory monitoring data in humans for the two-treatment regimen exposure are needed. These data were not submitted to the NDA in support of the AK indication. These data may already be available to the Sponsor from the basal cell carcinoma indication studies.

3. Please address cross-sensitivity between methyl-ALA and the currently marketed ALA product.

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)**

DATE RECEIVED: April 29, 2002

DUE DATE: June 5, 2002

ODS CONSULT #: 01-0218-1

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

*cc: Vaughan
Lutke
Vidra*

THROUGH: Vickey Lutwak
Project Manager
HFD-540

PRODUCT NAME:
Metvix
(Methyl Aminolevulinate Cream) 168 mg/gram

NDA SPONSOR:
Clementi & Associates for PhotoCure ASA
Hofffsveien 48
N-037 Oslo
Norway

NDA: 21-415

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proprietary name Metvix. The proprietary name Metvix was reviewed by DMETS in December 2001 and found to be acceptable (OPDRA consult # 01-0218). At the time of the initial review the sponsor indicated that Metvix would not be dispensed in pharmacies but would be distributed directly to healthcare practitioners. Prescription analysis studies were not conducted during the initial review based on this information. The sponsor has since indicated that they are unsure of the distribution process for Metvix and thus the product may be dispensed directly to patients from pharmacies. Consequently, DMETS will re-review the proprietary name Metvix to determine if the name can be misinterpreted due to sound-alike or look-alike products.

DMETS RECOMMENDATION: After reviewing additional data pertaining to the potential distribution process of "Metvix", DMETS reverses its initial decision and does not recommend the use of the proprietary name "Metvix."

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 12, 2002

NDA # 21-415

NAME OF DRUG: Metvix (Methyl Aminolevulinate Cream) 168 mg/gram

NDA HOLDER: Clementi & Associates for PhotoCure ASA

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for a re-review of the proprietary "Metvix." The proprietary name "Metvix" was reviewed by DMETS in December 2001 and found to be acceptable. At the time of the initial review the sponsor indicated that "Metvix" would not be dispensed in pharmacies but would be distributed directly to healthcare practitioners. Prescription analysis studies were not conducted during the initial review based on this information. The sponsor has since indicated that they are unsure of the distribution process for "Metvix" and thus the product may be dispensed directly to patients from pharmacies. Consequently, DMETS will re-review the proprietary name "Metvix" to determine if the name can be misinterpreted due to sound-alike or look-alike products. During the first DMETS review (December 2001) the container labels, carton labeling, and package insert labeling were reviewed for safety issues relating to possible medication errors. DMETS identified several areas of possible improvement that might minimize potential user error and recommended labeling changes. Revised labels and labeling were not submitted with this consult.

PRODUCT INFORMATION

"Metvix" cream contains the active ingredient methyl aminolevulinate. "Metvix" cream, in combination with red light illumination using the CureLight lamp, is indicated for the treatment of non-hyperkeratotic actinic keratoses. Topical application of methyl aminolevulinate results in formation of photoactive porphyrins, which are localized specifically in pre-malignant and malignant tumors of epithelial origin. When photoactive porphyrins are exposed to light of an appropriate wavelength in the presence of oxygen, a photochemical reaction takes place. This results in the production of singlet oxygen, which destroys intracellular components, in particular the mitochondria, leading to cell death. The activation of photosensitizers with resultant cytotoxicity forms the basis of photodynamic therapy of pre-malignant or malignant cells. Thus, application of "Metvix" cream to actinic (solar) keratoses causes photosensitization confined to the target lesions. Subsequent illumination of lesions leads to destruction of target lesions without risk to surrounding normal skin.

Photodynamic therapy for actinic keratoses with “Metvix” cream is a two-stage process involving (1) superficial preparation of the lesions followed by application of “Metvix” cream to target lesions for 3 hours under occlusive dressing, and (2) removal of the dressing and rinsing off excess cream followed by illumination with red light of wavelength 570 to 670 nm and total light dose of 75J/cm², using a “CureLight lamp.” “Metvix” cream is not intended for use with any device other than the CureLight lamp. “Metvix” cream will be available in 2-gram tubes containing 168 mg of methyl aminolevulinate per gram.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to “Metvix” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

During the initial review, an Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name “Metvix.” Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified Mavik and Mentax as proprietary names that were thought to have the potential for confusion with “Metvix.” These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.
2. DDMAC did not have concerns about the name “Metvix” with regard to promotional claims.

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician’s Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

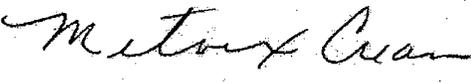
⁵ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

Product Name	Dosage form(s), Generic name	Usual adult dose	Other**
Metvix	Methyl Aminolevulinate Cream 168 mg/g 2 g tube	To be applied by trained personnel only. STEP A – Lesion should be debrided to remove scales and crusts and roughen the lesion surface. Apply a layer of Metvix cream about 1 mm thick to the lesion and surrounding skin. Cover with occlusive dressing for 3 hours. STEP B – Remove the dressing, clean the area with saline and gauze. Immediately expose the lesion to red light with a continuous spectrum of 570 to 870 nm and a total light dose of 75J/cm ² . Metvix cream is intended for use with only a "CureLight" lamp.	
Mavik	Trandolapril Tablets 1 mg; 2 mg; 4 mg	1- 4 mg by mouth once daily.	S/A and L/A
Mentax	Butenafine HCL Cream 1% 15 g tube; 30 g tube	Interdigital tinea pedis: apply twice daily for 7 days, or once daily for 4 weeks; Tinea corporis or tinea cruris: apply once daily for 2 weeks.	S/A and L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

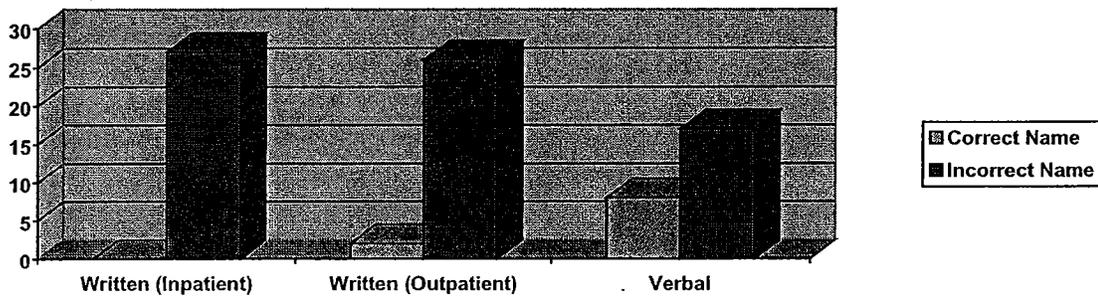
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Metvix" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 109 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Metvix" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient prescription was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretation of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Metvix Cream Dispense one tube Use as directed
Inpatient RX: 	

2. Results:

The results are summarized in Table II.

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	40	27 (68%)	0	27
Written Outpatient	36	28 (78%)	2	26
Verbal	33	25 (76%)	8	17
Total	109	80 (73%)	10	70



In the verbal study 17 of 25 (68%) participants interpreted “Metvix” incorrectly. The majority of the incorrect name interpretations were phonetic variations of “Metvix.” Ten of the seventeen (59%) incorrect interpretations involved the names Metvicks (4), Metvic (4), and Metvick (2). Seven other variations included Meczix (1); Metrick (1), Mexvik (1), Metzix (1), Vetnix (1), and Metsix (1). None of the misinterpreted names were similar to an approved product.

Among the two written studies, 53 of 63 (84%) participants interpreted the name incorrectly. Two respondents misinterpreted the name as currently marketed products. One respondent misinterpreted the prescription as metronidazole, while the other misinterpreted the prescription as Mentax. The most common variations of “Metvix” were: Metrix (19) or Metvex (7). Other incorrect interpretations included Mitrix (2), Metrex (2), Mitrex (2), and Metux (2). Seventeen single responses involved various spellings of “Metvix.” Moreover, Mentax is one of the names identified during the Expert Panel discussion as having the potential for name confusion.

C. SAFETY EVALUATOR RISK ASSESSMENT

During the initial review of the proprietary name “Metvix,” the primary concerns raised were related to two sound-alike and/or look-alike names: Mavik and Mentax. These names were also identified in this review as well. However, DMETS determined that the potential for confusion between “Metvix” and Mentax was reduced due to differences in dosage form (tablet vs. cream), route of administration (oral vs. topical), dosage, and frequency. DMETS’ previous assessment of “Metvix” and Mentax noted that there were similarities but that “Given the controlled supervised setting in which Metvix will be used, the risk of Metvix and Mentax being used in error is reduced.” This conclusion was based on the fact that “Metvix” would only be distributed to trained healthcare practitioners and would not be available via prescription. Since the distribution process of “Metvix” is uncertain, the analysis of potential name confusion between “Metvix” and Mentax has to be re-assessed.

Both “Metvix” and Mentax begin with the letters ‘me’ and end with the letter ‘x’ and contain the same number of characters—six. Additionally, both products have the letter ‘t’ in the middle of the name. These similarities may contribute to misinterpretation of “Metvix” and Mentax prescriptions when scripted and upon verbal pronunciation. “Metvix” and Mentax are both dermatological creams that will be applied topically. Although the dosing intervals differ between “Metvix” and Mentax, topical creams are often written with ‘use as directed’ instructions. Physicians may write ‘use as directed’ on “Metvix” prescriptions because they have counseled patients about returning to the office with the medication. Although “Metvix” is available as a 2 gram tube and Mentax as 15 and 30 gram tubes, the dispensing quantity may be written as ‘#1’ in lieu of the actual packaging quantity. These additional similarities increase the risk that these products may have a higher potential for confusion.

“Metvix” will be stored in the refrigerator and probably will not be routinely dispensed in pharmacies. One would think that this would help to reduce the potential for medication errors between “Metvix” and Mentax. However, differences in storage conditions do not always eliminate the risk of error. Post-marketing experience has demonstrated that errors occur between sound-alike and look-alike names despite the differences in physical characteristics or storage conditions. These differences may contribute to potential errors because practitioners may be more familiar with Mentax—a commonly used product—and therefore cognitively misinterpret a “Metvix” prescription for Mentax. Additionally, if the prescription has been cognitively misinterpreted, differences in physical characteristics or storage conditions would not prompt the practitioner that an error has occurred. Moreover, name confusion or cognitive errors between “Metvix” and Mentax may also occur during the restocking of pharmacy or nursing storage bins. This type of error could result in decreased “Metvix” potency, since approximately 20-30% of “Metvix’s” efficacy is lost if stored at room temperature for more than three months.

DMETS also conducted prescription analysis studies to determine if “Metvix” could be confused with Mentax. The majority of the respondents in the written studies interpreted the “Metvix” prescription incorrectly. One of these respondents interpreted the proposed name as Mentax. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. We also note that the prescription was written with ‘UD’ as the instructions for use and a dispensing quantity of ‘#1.’ The numerous similarities noted between “Metvix” and Mentax may increase the potential risk of name confusion between the two products.

III. COMMENTS TO THE SPONSOR:

The Division of Medication Errors and Technical Support does not recommend the use of the proprietary name Metvix. The primary concern is related to a name that already exists in the US marketplace, Mentax. DMETS' previous assessment of Metvix and Mentax noted that there were similarities but the risk of Metvix and Mentax being used in error was reduced due to the controlled supervised setting in which Metvix will be used. This conclusion was based on the fact that Metvix would only be distributed to trained healthcare practitioners and would not be available via prescription. DMETS re-assessed the potential name confusion between Metvix and Mentax based on the possibility that Metvix will be distributed via prescription.

Both "Metvix" and Mentax begin with the letters 'me' and end with the letter 'x' and contain the same number of characters—six. Additionally, both products have the letter 't' in the middle of the name. These similarities may contribute to misinterpretation of "Metvix" and Mentax prescriptions when scripted and upon verbal pronunciation. "Metvix" and Mentax are both dermatological creams that will be applied topically. Although the dosing intervals differ between "Metvix" and Mentax, topical creams are often written with 'use as directed' instructions. Physicians may write 'use as directed' on "Metvix" prescriptions because they have counseled patients about returning to the office with the medication. Although "Metvix" is available as a 2 gram tube and Mentax as 15 and 30 gram tubes, the dispensing quantity may be written as '#1' in lieu of the actual packaging quantity. These additional similarities increase the risk that these products may have a higher potential for confusion.

"Metvix" will be stored in the refrigerator and probably will not be routinely dispensed in pharmacies. One would think that this would help to reduce the potential for medication errors between "Metvix" and Mentax. However, differences in storage conditions do not always eliminate the risk of error. Post-marketing experience has demonstrated that errors occur between sound-alike and look-alike names despite the differences in physical characteristics or storage conditions. These differences may contribute to potential errors because practitioners may be more familiar with Mentax—a commonly used product—and therefore cognitively misinterpret a "Metvix" prescription for Mentax. Additionally, if the prescription has been cognitively misinterpreted, differences in physical characteristics or storage conditions would not prompt the practitioner that an error has occurred. Moreover, name confusion or cognitive errors between "Metvix" and Mentax may also occur during the restocking of pharmacy or nursing storage bins. This type of error could result in decreased "Metvix" potency, since approximately 20-30% of "Metvix's" efficacy is lost if stored at room temperature for more than three months.

IV. RECOMMENDATIONS:

DMETS does not recommend use of the proprietary name "Metvix".

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
6/12/02 01:25:30 PM
PHARMACIST

Carol Holquist
6/12/02 01:30:22 PM
PHARMACIST

Jerry Phillips
6/12/02 02:52:10 PM
DIRECTOR

NDA ORIG AMENDMENT
BM

CLEMENTI
& Associates

June 6, 2002

VIA FACSIMILE & FEDEX

RECEIVED

JUN 10 2002

MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

RE: Response to May 20, 2002 Questions (NDA 21-415)

Dear Dr. Wilken:

PhotoCure is responding to the Questions of the May 20 FDA Facsimile request. This request is derived from the TCON of May 30, 2002 and comments raised to PhotoCure's first response dated May 23, 2002.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 35)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIGINAL

REQUEST FOR CONSULTATION

TO (Division/Office):
Peter Cooney Ph.D.
HFD-160

FROM: HFD-540 Vickey Lutwak

DATE June 6, 2002	IND NO.	NDA NO. 21-415	TYPE OF DOCUMENT Attachments	DATE OF DOCUMENT
NAME OF DRUG 5-Aminolevulinic Acid		PRIORITY CONSIDERATION Yes. Continuing issue of sterilization	CLASSIFICATION OF DRUG Keratolytic for Actinic Keratoses	DESIRED COMPLETION DATE 7/26/02 PDUFA

NAME OF FIRM: Clementi & Associates, Ltd, US agents for Photocure

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Note: I have attached scanned in pages and inserted the file containing the new cleaning procedure
Brenda Vaughan, M.D. is the reviewer.

Two Issues.

1. The sterilization of the cream- attached /Dr. Vaughan's memo and the composition of the cream with the specs provided by the chemist, Jim Vidra.

the cleaning of the probe between patients. E-file attached. Is this adequate?

SIGNATURE OF REQUESTER
Vickey Lutwak, PM, HFD 540 7-2073

METHOD OF DELIVERY (Check one)

MAIL

HAND

Our Division is reviewing NDA 21-415 for treatment of actinic keratoses of the face and scalp using photodynamic therapy. This is a drug-device product (methyl aminolevulinate in combination with illumination with a PhotoCure Lamp) in which the drug product is not sterile and is not intended to treat wounds (actually causes epidermal cell destruction). The treatment procedures cause both mechanical and phototoxic damage to the epidermis.

The drug product is to be applied to multiple sites on the face and scalp (no limit on the number of treatment sites are specified in the proposed label). In one study conducted in the U.S., treatment was limited (4 to 10 lesions); however, in an Australian study up to 22 lesions were treated in one patient. In the U.S. study, lesion diameter before treatment ranged from 3 to 35 mm (the largest diameter of each lesion measured). The mean lesion diameter per patient ranged between 3.3 and 16.0 mm with a mean value of 7.4 mm.

Lesions are debrided with a small dermal curette to remove scales and crusts and roughen the surface. The drug product is applied to the prepared sites and then an occlusive dressing (Tegaderm®) is applied for approximately 3 to 4½ hours. According to the protocol, the drug product is then gently wiped off with non-sterile gauze dipped in a non-sterile saline solution (0.9% sodium chloride) prior to illumination (red light in the range of 570 to 670 nm).

A second treatment session consisting of the same procedure is repeated in 7 days. Illumination causes a local phototoxic reaction resulting in additional epidermal damage. Reported local adverse events (e.g., blisters, skin ulceration, bleeding, crusting, etc.) might be present at the second treatment session.

Under the proposed conditions of use: 1) should the drug product be sterile if applied to single or multiple abraded or ulcerated skin areas and 2) should sterile gauze and sterile saline solution be used?

H

2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

May 28, 2002

VIA FACSIMILE & FEDEX

RECEIVED
MAY 29 2002
MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

RE: Response to May 14, 2002 Question 4 (NDA 21-415)

Dear Dr. Wilken:

PhotoCure is responding an update to Question 4 of the May 14 FDA Facsimile request. The information provided in the original submission of May 23rd (356h 031) contained only one side of the two sided data. The attached response providing the two sided data (in one side format) is appended.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 34)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIG AMENDMENT

BM



RECEIVED

MAY 28 2002

May 24, 2002

MEGA/CDER

VIA FACSIMILE & FEDEX

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

RE: Response to May 21, 2002 Questions (NDA 21-415)

Dear Dr. Wilken:

PhotoCure is responding to the Request for Information that was received from the Division via facsimile on May 21, 2002. The response providing information is appended.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,

A handwritten signature in black ink, appearing to read "W. Clementi", with a large, sweeping flourish at the end.

William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 33)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIG AMENDMENT

BC

CLEMENTI
& Associates

May 23, 2002

VIA FACSIMILE & FEDEX

RECEIVED

MAY 24 2002

MEGACDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

RE: Response to May 14, 2002 Questions (NDA 21-415 Serial #031)

Dear Dr. Wilken:

PhotoCure is responding to the Request for Information that was received from the Division via facsimile on May 14, 2002. The response providing information is appended.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D., F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 31)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIGINAL



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 5-20-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	

Total no. of pages including cover: 2

Comments: Please see following page. If you have any question, please call me.

We would like to resolve this issue as soon as possible. Please let me know when we can expect a response. Thank you.

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-415 Metvix: Clinical Request

Please respond with a discussion of the following safety issue. Both the instructions and
are inadequate for between patient use.
It appears that curettage for lesion preparation followed by the placement of the diode at
the lesion surface may cause the diode to be placed in contact with human body fluids.
Since an open wound may be produced there may be exposure to blood and it is possible
that the diode may be coated with blood borne bacterial and viral pathogens. The next
patient would possibly have an open wound exposed to infection with the pathogen
adhering to the diode.

Additionally, it is unclear whether the horseshoe-shaped positioning device is also placed
on or at the skin surface. Since multiple treatment fields are possible, the horseshoe-
shaped positioning device could also be in contact with open wound areas.

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 5-14-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak VL
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	

Total no. of pages including cover: 2

Comments: Please respond to the following request for information from the chemistry reviewer.

We would like to know when to expect a response for time is growing short.

If you have any question, please call me. VL

Document to be mailed: YES NO

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NDA 21-415
METVIX
May 14, 2002

Request for information:

1. Submit to the Agency all accelerated and long-term stability data on the Modified/Optimized Metvix Cream batches as the data becomes available.
2. Although the submitted _____ specifications follow _____
Please provide the following missing tests: _____
3. Please resubmit the _____ Study located in the drug substance stability protocol, v4, page 171. Only one side of two-sided pages were previously submitted.
4. When conducting stability studies in the _____ drug substance _____, please follow the ICH time points and not the stated timepoints.
5. The contact name, full address, telephone and fax numbers at the drug product's manufacturing facility were not submitted as previously requested.
6. Please convert from area % to % wt/wt for the impurities _____ (v6, pages 128-135) to determine what an _____ is comparable to in % wt./wt.
7. The applicant should determine the amount of _____ remaining at the end of the expiration date. If the _____ is reduced below the lower specification limit of _____ w/w, then another preservative system should be considered.

CLEMENTI
& Associates

May 6, 2002

ORIGINAL

VIA FACSIMILE & FEDEX

RECEIVED

MAY 07 2002

MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

BS

NDA ORIG AMENDMENT

RE: NDA 21-415 Response to FDA FAX 05-02-02

Dear Dr. Wilken:

PhotoCure is responding to the Clarification Request for information that was received from the Division via facsimile on May 2, 2002. The attached information provides more information in order for the Division to complete its review of outstanding issues.

This submission completes all outstanding questions that have been received from the Division for the above referenced NDA. If there are any new questions, please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 28)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

CLEMENTI
& Associates

RECEIVED

May 3, 2002

MAY 06 2002

VIA FACSIMILE & FEDEX

MEGA/CDER

ORIGINAL

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

BB
NDA ORIG AMENDMENT

RE: Response to March 18th, 2002 Questions (NDA 21-415 Serial #029)

Dear Dr. Wilken:

PhotoCure is responding to the Biopharmaceutics Request for information that was received from the Division via facsimile on March 18, 2002.

The March 18, 2002 correspondence from the Division included two requests for information. PhotoCure is providing detailed information in response to each question. Each question from the Division is presented in bold italicized type, followed by the PhotoCure response in unbolded and non-italicized type. A table of contents is attached.

Data listings from Study PC T206/98 are presented as original listings (so labeled) and then re-formatted to include column headings.

All information provide in this documentation either written or in electronic format (diskette or CD Rom) is to be treated as Confidential.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 29)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 05-02-02

To: William Clementi, Pharm.D.

From: Victoria Lutwak 

Company: Photocure ASA

Division of Dermatological and Dental
Drug Products

Fax number: 610-581-7025

Fax number: 301-827-2075/ 827-2091

Phone number: 610-581-7021

Phone number: 301-827-2073

Subject:

Request for information for NDA 21-415 follow-up to your fax of 4/19/02.

I would like a to know when this information will be available for the statistician.

Please let me know your proposed timeline for submission.

If you have any question, please call. Thank you.

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed:

YES

NO

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NDA 21-415
METVIX

The Agency made a request to the Sponsor on the randomization procedure for study PC T302. The Sponsor's responses were submitted via fax on 4/19/02. The Agency has reviewed the submission. The Agency requests clarification concerning the following points related to the Sponsor's submission of 4/19/02.

- The Sponsor indicated that patients were allocated sequentially within center and stratum. However, one shipment of medication packed according to the randomization list was allocated for center 4 (—), but later was re-labeled for use at center 1 (—) (i.e. patient IDs: 4006, 4007, 4008, 4009 and 4029). Please clarify such change in treatment package allocation.
- Subjects 4013, 4014, 4015, and 4016 had 2, 1, 1, and 1-baseline AK lesions (pages 295-300, Volume 49, and Sponsor's SAS electronic data sets). However, they were randomized based on the stratum of baseline lesion number category 4-7 (submission dated 4/19/02). On the other hand, subjects 4025, 4026, 4027 had 1, 3, and 3 baseline AK lesions. However, they were randomized based on the stratum of baseline lesion number category 8-10. Please clarify why these patients were not in the correct strata.

Request for information for NDA 21-415 follow-up to your fax of 4/19/02.

We would like to know when this information will be available for the statistician.

Please let me know your proposed timeline for submission.

If you have any question, please call. Thank you.

**APPEARS THIS WAY
ON ORIGINAL**

CLEMENTI
& Associates

April 26, 2002

VIA FACSIMILE & FEDEX

ORIGINAL

RECEIVED

APR 29 2002

MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

NDA ORIG AMENDMENT

RE: Response to March 28th, 2002 Questions (NDA 21-415 Serial #027)

Dear Dr. Wilken:

PhotoCure is responding to the Clinical Request for information that was received from the Division via facsimile on March 28, 2002.

The March 28, 2002 correspondence from the Division included five requests for information from studies PC T302, PC T305 and PC T306. Subsequently, the Division issued another correspondence on April 10, 2002 (after question clarification requests to the Division by PhotoCure ASA), which repeated the five earlier requests for information on lesion thickness and size of fields, and requested additional information on fields from these three studies. The new requests were for information on fields for: non-complete responders overall, thin lesions in non-complete responders, moderately thick lesions in complete responders, moderately thick lesions in non-complete responders, and thick lesions in non-complete responders. The present submission includes the request from the March 28, 2002 correspondence as clarified on April 10, 2002.

In the attached document each question from the Division is presented in bold italicized type, followed by the PhotoCure response in unbolded and non-italicized type.

All information provide in this documentation either written or in electronic format (diskette or CD Rom) is to be treated as Confidential.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 27)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

CLEMENTI
& Associates

RECEIVED

April 19, 2002

APR 22 2002

MEGA/CDER

VIA FACSIMILE & FEDEX

NDA ORIG AMENDMENT

BB

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

RE: Answers to March 26th Questions (NDA 21-415)

Dear Dr. Wilken:

PhotoCure is responding to the questions asked and submitted to us by FAX (only) by the Division on March 26th, 2002. In addition, a 3-½ inch floppy disk containing the electronic version in MS Word format of the two pharmacokinetic studies, PC T101/97 and PC T206/97, are included, as requested.

All information contained herein written or on computer diskette is Confidential.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 25)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIGINAL

CLEMENTI
& Associates

NDA ORIG AMENDMENT

April 18, 2002

BM

VIA FACSIMILE & FEDEX

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APR 19 2002

MEGA/CDER

Richard Felton
Food And Drug Administration (HFZ-410)
CDRH, Room 310K
9200 Corporate Blvd.
Rockville, MD 20850

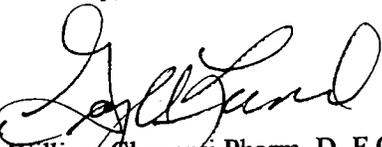
RE: Illumination and Total Energy References

Dear Mr. Felton:

The attached two literature references are provided for your review of NDA Item 32H Clinical Data. References 5, 6 and 7 were provided earlier. These references are the same that were provided in Item 6B concerning the choice of light dose: "Choice of Fluence Rate of Illumination and Total Energy Delivered: (Reference Number 24, 25, 26, 27 and 28).

If you have any additional, questions please call (610) 581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent PhotoCure

cc: US and Norway Regulatory Files
FDA Form 356h (No: 26)

Desk Copy to Ms. V. Lutwak, FDA

ORIGINAL

April 16, 2002

VIA FACSIMILE & FEDEX

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APR 19 2002
MEGA/CDER

ORIGINAL ^{NC}
NEW CORRESP

Richard Felton
Food And Drug Administration (HFZ-410)
CDRH, Room 310K
9200 Corporate Blvd.
Rockville, MD 20850

RE: Facilities Inspection

Dear Mr. Felton:

The attached information is provided for your information and review per the Division's request for information pertaining to the facilities and quality programs at PhotoCure ASA Norway.

If you have any additional questions please call (610) 581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent PhotoCure

cc: US and Norway Regulatory Files
FDA Form 356h (No: 23)

Desk Copy to Ms. V. Lutwak, FDA

April 12, 2002

NEW CORRESP
NC

VIA FACSIMILE & FEDEX

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APR 17 2002

MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

RE: Questions for TCON April 15, 2002 (10:00 AM EDT)

Dear Dr. Wilken:

PhotoCure would like to propose that the Division address the following questions during the TCON scheduled for 10:00 AM on April 15, 2002.

1. PhotoCure is concerned that we have not had any notification of clinical data inspection dates. Chemistry and devices have communicated dates so far and we are scheduled for June. When can we expect the clinical inspections to occur?
2. Dr. Vaughn asked this week if the distribution of Metvix[®] Cream was to pharmacies or doctor's offices. Could she elaborate on the importance of this question?
3. PhotoCure would like to discuss the implications regarding the review of the new "numerical analysis" because PhotoCure has not been requested to impart an explanation or interpretation of these new analysis.

If you have any additional questions please contact me at (610) 581-7021.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 24)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

ORIGINAL



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5**

FACSIMILE TRANSMITTAL SHEET

DATE: 4-10-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject: Clarification of previous fax dated March 28, 2002, clinical request for information.

Total no. of pages including cover: 4

Comments: Please see following page(s).

Document to be mailed: YES NO

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NDA 21-415
METVIX

21-415 Metvix: Clinical Request (Clarification 041002)

Please provide the following information for each study: 302; 305; and 306, where available. Your response #2 on the fax of April 05 seems reasonable.

Please understand that this is NOT a request for new analysis. This is a request for presentation of existing information. Presentation in histogram format would be particularly useful.

Information on fields

1. Numbers of patients (N) in each of the following categories:

- One lesion/field
- Two lesions/field
- Three lesions/field
- Four lesions/field
- Five lesions/field
- Six lesions/field
- 7-10 lesions/field
- 10-15 lesions/field
- >15 lesions/field.

2. Number of patients (N) in each of the following categories:

- Only one field treated
- Only two fields treated
- Only three fields treated
- Only four fields treated
- Only five fields treated
- More than five fields treated

Information on responders/non responders grouped by lesion size. (please include the sample size when providing this information for each table)

3. For the patients considered complete responders, please provide the total number of lesions treated in each of the following discrete categories (i.e all lesions in each category cleared completely).

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm

- Lesion size 11-12mm
 - Lesions >12mm
4. For the patients considered non- complete responders, please provide the total number of lesions treated in each of the following discrete categories . (Please also provide the number of lesions that cleared, and the number that did not clear.)
- Lesion size 3-4mm
 - Lesion size 5-6 mm
 - Lesion size 7-8 mm
 - Lesion size 9-10mm
 - Lesion size 11-12mm
 - Lesions >12mm

Lesion thickness tabulations: (please include the sample size when providing this information for each table)

5. Thin Lesions: For patients considered complete responders, please provide the total number of thin lesions treated in each of the following discrete categories
- Lesion size 3-4mm
 - Lesion size 5-6 mm
 - Lesion size 7-8 mm
 - Lesion size 9-10mm
 - Lesion size 11-12mm
 - Lesions >12mm
6. Thin Lesions: For patients considered non- complete responders, please provide the total number of thin lesions treated in each of the following discrete categories
- Lesion size 3-4mm
 - Lesion size 5-6 mm
 - Lesion size 7-8 mm
 - Lesion size 9-10mm
 - Lesion size 11-12mm
 - Lesions >12mm
7. Moderately thick Lesions: For patients considered complete responders, please provide the total number of moderatley thick lesions treated in each of the following discrete categories

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm
- Lesion size 11-12mm
- Lesions >12mm

8. Moderately thick Lesions: For patients considered non-complete responders, please provide the total number of moderately thick lesions treated in each of the following discrete categories

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm
- Lesion size 11-12mm
- Lesions >12mm

9. Thick Lesions: For patients considered complete responders, please provide the total number of thick lesions treated in each of the following discrete categories

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm
- Lesion size 11-12mm
- Lesions >12mm

10. Thick Lesions: For patients considered non-complete responders, please provide the total number of thick lesions treated in each of the following discrete categories

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm
- Lesion size 11-12mm
- Lesions >12mm

April 7, 2002

VIA FACSIMILE & FEDEX

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APR 10 2002

MEGA/CDER

BC
NEW CORRESP

James Vidra Ph.D.
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
Food and Drug Administration (HFD 580)
5600 Fishers Land
Rockville, MD 20857

Re: Drug Substance Facilities Inspection

Dear Dr. Vidra:

The information provided below is in reference to our telephone conversation of April 4, 2002 concerning the upcoming inspection of the facilities. The name of the person to contact, the address and telephone number are shown below.

Contact Person:
Direct Telephone:

Company Name:

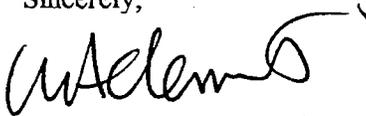
Visiting Address:

Telephone:

Facsimile

If you need help in making hotel reservations or have any additional questions please call (610) 581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent PhotoCure

cc: US — Regulatory Files
FDA Form 356h (No: 22)
Desk Copy to Ms. V. Lutwak, FDA

Friday, April 05, 2002

VIA FACSIMILE & FEDEX

ORIGINAL

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APR 09 2002

MEGA/CDER

NC

NEW CORRESP

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-415 (PhotoCure is requesting Clarification of Reviewer's Request on Clinical Items referencing Questions Provided to PhotoCure on March 28, 2002)

Dear Dr. Wilken:

Clinical reviewers have asked PhotoCure to perform additional analyses of patient complete response rate according to lesion size and depth. These analyses were not planned as part of the original statistical plans in the protocol and accordingly, PhotoCure is requesting clarification while specifying its own recommendation for further analyses. The reviewers have asked that all patients should be categorised into intervals of lesion size and description (thin and thick lesions). It is unclear how to select patients for such intervals because patients have had more than one lesion of varying degrees.

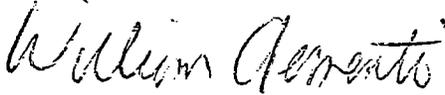
Questions Intended to Clarify Reviewer's Request:

- 1) How shall we categorise a patient with multiple lesions of different size and description into one category? For example, a patient with two thin lesions, one lesion with a size 7 mm, and one with a size of 11 mm could be categorised to either category 7-8 mm or to category 11-12 mm. PhotoCure proposes to use the mean value of lesions within the patient as the basis for these new analyses.
- 2) The question from the Division only referred to thin and thick lesions without referring moderately thick lesions. Only PhotoCure study PC T 302/99 included thick lesions. Based the design of the studies PhotoCure wishes to include three groups rather than two groups; these groups are thin, moderately thick and thick lesions? Is the reviewer in agreement with this approach?

PhotoCure is requesting a prompt response to this letter so that the appropriate programming can be initiated. PhotoCure is willing to participate in a TCON if necessary, as PhotoCure believes these new analyses may contain informative results but that such results post hoc must have cautious interpretations.

We look forward to hearing from the Division as soon as possible.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates
US Agent for PhotoCure ASA

CC: Regulatory Files US and Norway
FDA Form 356h (No: 21)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak

CLEMENTI
& Associates

April 2, 2002

VIA FEDEX

ORIGINAL

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APR 08 2002

MEGA/CDER

Jonathan Wilken M.D.
Director
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research)
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Be
NDA ORIG AMENDMENT

Re: NDA 21-415 (Answers to February 11, 2002 CMC Questions)

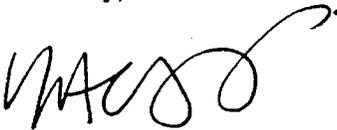
Dear Dr. Wilkin:

Attached is the PhotoCure response to the Division's Chemistry, Manufacturing and Control questions of February 11, 2002. This submission is within the time frame specified by the Division which required the answer is submitted not later than April 15, 2002.

This submission is organized into two sections, questions regarding Drug Substance and Drug Product. In each section, the reviewer's questions are in italics and PhotoCure's response is written below each question. References to the NDA are specified with the volume and page numbers. There are six enclosures (Tabulated and Marked) for the Drug Substance section and eight enclosures (Tabulated and Marked) for the Drug Product section.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William A. Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd
US Regulatory Agent PhotoCure ASA

cc: US and Norway Regulatory Files
FDA Form 356h (No: 20)

VIA FACSIMILE, Cover Letter to Ms. V. Lutwak



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 3-28-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	

Total no. of pages including cover: 4

Comments: Please see following page(s). If you have any question, please call me.

In addition, please estimate when we can expect a response to this request. Thank you.

Document to be mailed: YES NO

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NDA 21-415 Metvix: Clinical Request

Lesion preparation procedures and Illumination

1. Who demonstrated the treatment procedure (lesion preparation, cream application and removal and the illumination procedure) to the investigators and/or study nurses for Study PC T306, Study PC T305, and Study PC T302?
2. Please provide information for setting the parameters of the lamp (e.g., distance, number of lesions per field, and treatment time, etc.).
3. Were patients treated simultaneously with two lamps? The Sponsor provided each center with two lamps for Study PC T306 (Vol. 1.22, pg. 17) and Study PC T305 (Vol. 1.25, pg. 18). Please provide the rationale for providing each center with two lamps.
4. (Vol. 1.24, Listing 10) Water spray and fan were used during treatment for Patients 5002, 5004, 5007, & 5012. Were all investigators instructed to use water spray and fan during treatment for patient discomfort?

Study PC T306/99

1. Who monitored local adverse events for safety and administered medical treatment? According to the submission (Vol. 1.22, pg. 20 & 21), the study nurse administered the light treatment and recorded local adverse events.
2. Please provide Case Report Forms (including photographs) for the following patients: 2003, 2006, 2021, 3001, 3003, 3005, 3006, 4002, 4004, 4010, 4011, 4012, 4016, 4017, 4018, 5001, and 5004.
3. Who performed the two-week lesion and safety evaluation after the second PDT treatment session?
4. What were the instructions for the number of treatment fields per session and where in the NDA submission are these data recorded? The protocol for Study PC T306/99 is silent regarding the number of treatment fields as opposed to Amendment 1 for Study PC T305 where all eligible lesions were to be treated using no more than 6 circular fields with maximum diameter of 5.5 cm (Vol. 1.25, pg. 16).

Study PC T 305/99

Requesting the following:

1. Please provide a detailed explanation for Tables 13 –16 (Vol. 1.25).
2. Please provide the address for Site #1 where the study was conducted.
3. Difference between Lead Investigator and PI (principal investigator)?
4. Where in the submission is the CV for _____ located?
5. Please provide the study site address for Site #007.
6. How do the extent and severity of actinic keratoses in Australian and European population compare to the US population? According to Vol. 1.25, page 16, "...the extent and severity of actinic keratoses in Australian patients is different from that seen in most European patients."
7. Case Report Forms (including photographs) for the following patients: 1014, 8011, 1015, 9026, 9031, 7004, 6006, and 1019.

Study PC T 302/99

Please provide an electronic copy in Word of the Clinical Trial Report for study PC T302/99.

Studies 302; 305; and 306

Please provide the following information for studies 302; 305; and 306.

1. Numbers of patients (N) in each of the following categories:
 - One lesion/field
 - Two lesions/field
 - Three lesions/field
 - Four lesions/field
 - Five lesions/field
 - Six lesions/field
 - 7-10 lesions/field
 - 10-15 lesions/field
 - >15 lesions/field.

2. Number of patients (N) in each of the following categories:
 - Only one field treated
 - Only two fields treated
 - Only three fields treated
 - Only four fields treated
 - Only five fields treated
 - More than five fields treated

3. ALL PATIENTS: Number of patients considered complete responders and total number treated in each of the following discrete categories (place pts into one category only):
 - Lesion size 3-4mm
 - Lesion size 5-6 mm
 - Lesion size 7-8 mm
 - Lesion size 9-10mm
 - Lesion size 11-12mm
 - Lesions >12mm

4. Thin Lesions: Number of patients considered complete responders and total number treated in each of the following discrete categories (place pts into one category only):
 - Lesion size 3-4mm
 - Lesion size 5-6 mm
 - Lesion size 7-8 mm
 - Lesion size 9-10mm
 - Lesion size 11-12mm
 - Lesions >12mm

5. Thick Lesions: Number of patients considered complete responders and total number treated in each of the following discrete categories (place pts into one category only):

- Lesion size 3-4mm
- Lesion size 5-6 mm
- Lesion size 7-8 mm
- Lesion size 9-10mm
- Lesion size 11-12mm
- Lesions >12mm

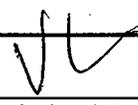
**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 3-26-2002

To: William Clementi, Pharm.D.	From: Victoria Lutwak 
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject:

Request for information for NDA 21-415
We would like a to know when this information will be available for the statistician. Please let me know your proposed timeline for submission for these request from the statistician and biopharm reviewers
Thank you.

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: YES NO

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NDA 21-415 Metvix Cream

Statistician's request for information:

Concerning the randomization for study PC T302/99, please provide the following items:

1. Please explain whether the randomization was done prior to patient enrollment in the trial based on computer generated list. If so, please provide such treatment allocation list.
2. How many centers were planned to participate in the trial and number of patients planned to be enrolled in each center?
3. Please explain whether randomization was done centrally (i.e. study level) or on the investigator level (i.e. randomization was done per investigator basis). Please explain any deviations from the pre-planned randomization procedure.
4. If patient allocations were not in sequence, please provide an explanation on such cases.

Biopharm request for e-files:

Can you provide an electronic version (preferably in MS Word format) of the two PK studies (101/97 and 206/98)?

REQUEST FOR CONSULTATION

TO (Division/Office):
Peter Cooney Ph.D.
HFD-160

FROM: HFD-540 Vickey Lutwak

DATE March 26, 2002	IND NO.	NDA NO. 21-415	TYPE OF DOCUMENT User Manual /PhotoCure	DATE OF DOCUMENT
NAME OF DRUG 5-Aminolevulinic Acid		PRIORITY CONSIDERATION Yes. Just found this issue buried in the manual.	CLASSIFICATION OF DRUG Keratolytic for Actinic Keratoses	DESIRED COMPLETION DATE 7/26/02 PDUFA

NAME OF FIRM: Photocure

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

Brenda Vaughan, M.D. is the reviewer.

A light measuring diode device is being used for calibration prior to illumination with PhotoCure 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)

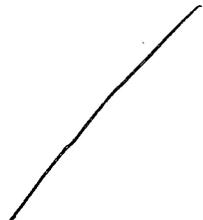
According to the User Manual (pg. 11), calibration should be performed with the light measuring diode placed at the lesion surface prior to illumination. There is a concern that lesion preparation might produce an open wound and some bleeding since lesion preparation consists of debriding with a small 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.

Is the Sponsor's plan adequate for between patient disinfecting of the light measuring diode? A copy of the user manual is attached.

ground

According to the proposed Dosage & Administration Section of the label for NDA 21-415:



According to the protocol, lesion preparation was as follows:

Prior to administration of Metvix[®] or placebo cream, the lesion was prepared in order to facilitate access of Metvix[®] and light to all parts of the lesion. Preparation of the lesion, when applicable, was performed before each treatment. The extent of preparation depended on the nature of the lesion. Scales and crusts were to be removed to ensure that illumination was not blocked. Scales and crusts were removed by a small dermal curette and the surface of the lesion was scraped gently in order to roughen the surface.

SIGNATURE OF REQUESTER

Vickey Lutwak, PM, HFD 540 7-2073

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 3-¹⁷~~18~~-02

To: William Clementi, Pharm.D.	From: Victoria Lutwak VL.
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject: Request for information for NDA 21-415
 We would like a to know when this information will be submitted to the NDA.
 If it has already been submitted, please tell us the location-- volume number and page.
 Thank you. *Videeb*

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-415
METVIX

REQUEST FOR INFORMATION:

Biopharm Request:

Calibration: In absence of any proper validation of skin fluorescence measurement data, the sponsor is asked to submit routine scheduled instrument calibration data. Also, a full report including full set of data (NOT the summary Table) conducted in the pilot study on three subjects is also requested.

Study 206/98: In report 1.10.99 entitled "A Pharmacokinetic study of PpIX formation in patients with AK and BCC after topical application of P-1202 cream" (Page 180, Vol. 18) Population PK analysis and modeling have been mentioned and pertinent information on this aspect is supposed to be included in AP1-9. However, the reviewer could not locate AP 1-9 in the submission. Hopefully the missing section will also contain individual patient data at each time point after application of each strength of cream, as only summary data could be found in Tables 7 - 15. Individual patient data on study 101/97 is also requested, if it has not been submitted yet.

February 19, 2002

PhotoCure ASA
c/o Dr. William A. Clementi, F.C.P.
Clementi & Associates
919 Conestoga Road
Rosemont, Pennsylvania 19010

Re: P010061
CureLight BroadBand Model CureLight 01
Filed: September 27, 2001

Dear Dr. Clementi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). CDRH is pleased to inform you that the PMA is approvable. Be advised that FDA is continuing to review your labeling and will communicate any remaining changes via phone and fax. Please submit the following:

1. Although you have provided some information regarding software validation in the manufacturing section of your application, Section 8.14.7 (Performance Validation) and Section 8.14.8 (Software Validation), this information does not meet the full requirement for software validation for your control module. We recommend that you obtain a copy of the document "Reviewer Guidance for Computer Controlled Medical Devices" which is available on the Center's web site. This document outlines the types of information required for software validation such as a hazard evaluation of the device, a written description of the system and software requirements, a description of how the software was developed, and a description of the validation process.
2. The describing your light system you have provided illustrations and discussion for the placement of IR and cooling mirrors within the light pathway. You have also provided a spectral output curve for you device showing the wavelength range of 570-650 nm. Please provide a description or discussion of how the wavelengths below 570 nm have been eliminated from the broad output wavelength of the halogen source lamp specifically the UV and blue wavelengths.

The PMA cannot be approved until an inspection has been conducted and FDA has determined that the manufacturing facilities, methods and controls comply with the conditions set forth in your application and the applicable requirements of the Quality System Regulation (21 CFR Part 820). If you have any questions regarding the status of your QSR inspection please contact your District Office or the Office of Compliance at (301) 594-4695.

In addition, prior to PMA approval, you must obtain approval from the Center for Drug Evaluation and Research on your NDA 21-415.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>

The PMA must be amended to include your concurrence with, or suggested revision of, the enclosed "Conditions of Approval." You may use the enclosed form for this purpose.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Following receipt of an approvable letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The clinical update must be consistent with the data reporting provisions of the protocol.

CDRH will issue an approval order after the requested information and inspectional findings have been reviewed and determined to be acceptable. You may not begin commercial distribution of the device until you have received an approval order and final printed labeling has been submitted to FDA.

You may amend your PMA as requested, or withdraw it, or you may treat this letter as a formal denial of approval. If you choose the latter, you may request administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(3) and 515(g) of the Federal Food, Drug, and Cosmetic Act by filing a petition with the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852, within 30 days of the date you receive this letter. A petition for administrative review must be submitted

in accordance with general administrative procedures for submission of documents to the Dockets Management Branch (21 CFR 10.20) and in the form of a petition for reconsideration (21 CFR 10.33). After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (3 copies), clinical data update (3 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies), or request an extension. The required copies of the amended PMA should include the FDA reference number to facilitate processing for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approvable letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours,

Division Director

Or

Deputy Office Director, if 1st of a kind

(see Blue Book Memo)

Enclosure

cc: HFZ-306 (Field Programs Branch - QSR)

HFZ-401 (Document Mail Center)

HFZ-402 (PMA Staff)

HFZ- [ODE DIVISION]

HFZ-542 (Statistics Staff)

HFZ-310 (Bioresearch Monitoring)

D.O.

Feb. 6, 2002

Dear Gary,

We have an additional request for information from Dr. Clementi.

Please provide a delineation of patients treated in 306 prior to the amendment of 7/17 (change of dosing).

Thank you.

Regards,

A handwritten signature in cursive script, appearing to read "Vickey".

Vickey

February 5, 2002

Review of P010061

Submitted by Clementi & Associates
for PhotoCure ASA

Reviewed by Richard P. Felten, DGRND, GSDB

This is the substantive review for this application for the device section. The device, which is the subject of this application, is the light activation source for a photosensitive drug and therefore, is part of a combination drug/device for which CDER has review lead. Therefore, labeling and instructions for use can not be finalized until CDER has made a final decision on labeling claims for the drug. Likewise issues regarding adverse events are also part of the CDER review and these issues will be transmitted to CDER for their consideration and transmittal to the company if deemed necessary by the CDER review team.

As mentioned in the November 8, 2001 review, the device, which is the subject of this application, is a broad spectrum light source intended to activate protoporphyrin IX which is generated within the actinic keratosis following application of methyl aminolevulinate to the skin surface. The actual activation wavelength, which is used to expose the treatment site is 570-650 nm. This wavelength is produced by passing the output of a halogen lamp through a series of IR filters, an aspheric focusing lens, and a cooling system. The system is capable of illuminating a 35-55 mm diameter spot. A calibration probe is provided as part of the system and this is placed into the proposed treatment field to allow the user to calibrate the light parameters to obtain the desired dose rate and total fluence which has been set at 200 mW/cm² and 75 J/cm² respectively.

The light output is control through a microprocessor control module. This module contains the on/off switch, a low light switch used for calibration, a calibration button for used to determine dose during calibration, a set dose button which allows adjustment of output to meet correct dose following calibration, and a full light button which is activated to produce the therapeutic treatment. The buttons are numbered to provide user guidance in the sequence each should be used to insure correct procedure for preparing the system for therapy. As part of the initial turn on of system, following initial warm-up the display will inform user of remaining lamp life. The lamps are designer for 50 hours of use.

The Operator Manual provides the step by step procedure for preparing the lamp for use, includes warnings regarding patient and user eye safety, has illustrations of the lamp and lamp assembly and provides directions for changing of the halogen lamp.

Review of this application has identified several device issues that need to be addressed. These issues are:

1. Company has not provided a specific software validation section for the control module. There is a section in the manufacturing section, which briefly mentions software validation, however this does not address the issue of microprocessor software as described in the Center's guidance on software validation. The manufacturing section mentions that there was a change in the multiplication table used to determine output but does not provide the types of information required for software validation such as a risk analysis, determination of software hazard level, how the software was written, and how it was validated. Company will be advised to obtain a copy of the Guidance for Software Review for 510(k)'s as the best way of proceeding for this issue.
2. Company has provided a spectral output curve for their light showing that the light is within the 570-650 nm range. In describing the light source company has shown where IR filters are placed. Company has not stated whether or not the halogen lamp produces any UV output and if it does how this is being filtered from system.
3. As with UV no mention is made of a filter to remove wavelengths below 570 nm that is the blue wavelengths. It might be that the band pass filters are part of the system which restrict light transmission to 570-650 nm but the description of the device only indicates IR filters present and a color filter at the bottom of the assembly.

A final decision on device labeling can not be made at this time, therefore there is no reason to request changes in Indications for Use or labeling within the Operator Manual until the final decision on approval is made by CDER. At this time this application is approvable with this information and this information does not constitute a major deficiency. Likewise a final decision cannot be made on this application until the manufacturing site GMP is completed.

Therefore, it is recommended that an Approvable letter with deficiencies be prepared for this application. Such a letter will notify company of the deficiencies that need to be addressed and at the same time stop the review clock, thus allowing time for final labeling changes once CDER has made their decision on the drug portion of this application.

CLEMENTI
& Associates

RECEIVED

January 17, 2002

JAN 25 2002

MEGA/CDER

N-000(SU)
ORIG AMENDMENT

Jonathan K. Wilkin M.D.
Division of Dermatologic & Dental Drug Products
Center for Drug Evaluation & Research (HFD-540)
9201 Corporate Blvd. (Room N-248)
Rockville, MD 20850

Re: NDA 21-415 Metvix[®] Cream PhotoCure ASA

Pursuant to CFR §314.50, 5(vi)(b) PhotoCure is submitting the 120 Day Safety Update for the above referenced NDA. The majority of information contained in this update reflects experiences in Basal Cell Carcinoma.

The Actinic Keratosis clinical development is complete and there are no ongoing studies in the United States. Changes in adverse event frequency have been of a small magnitude and predominately seen in the follow-up period in which the recurrence of new lesions and cosmetic outcome of treated lesions are evaluated. Serious adverse events that have been reported to the IND are included in this 120 Safety Update.

Data regarding the SAE for Patient #9004 (page 221 of this report) has been submitted on October 8, 2001 and a follow-up on January 24, 2002 for IND 59,221.

If you have, any questions do not hesitate to call.

Sincerely,



William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure ASA
cc: US and Norway Regulatory Files

ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:

October 24, 2001

DUE DATE:

December 24, 2001

OPDRA CONSULT #: 01-0218

TO:

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH:

Kalyani Bhatt
Project Manager
Division of Dermatologic and Dental Drug Products
HFD-540

PRODUCT NAME:

Metvix
(methyl aminolevulinate cream) 168 mg/g

NDA 21-415

MANUFACTURER:

PhotoCure ASA
Hoffsvveien 48
N-0377 Oslo
Norway

SAFETY EVALUATOR: Kevin Dermanoski, RPh

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products, OPDRA conducted a review of the proposed proprietary name, Metvix.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the proprietary name Metvix. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to its NDA approval will assess any safety risks based upon other proprietary names/NDA's that are approved subsequent to the date of this document. In addition, OPDRA recommends revising the container label, carton and insert labeling as outlined in Section III of this consult.

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 443-5161

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 20, 2001

NDA: 21-415

NAME OF DRUG: Metvix Cream 168mg/g

NDA SPONSOR: PhotoCure ASA
Hoffsvæien 48
N-0377 Oslo
Norway

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Products (HFD-540) to review the proposed proprietary drug name Metvix Cream 168mg/g, regarding potential name confusion with existing proprietary/established drug names. OPDRA also reviewed the proposed draft container label, carton and insert labeling.

PRODUCT INFORMATION

Metvix cream is an oil in water emulsion that is administered topically for photodynamic therapy (PDT). Metvix cream contains the active ingredient methyl aminolevulinate. Metvix cream, in combination with red light illumination using the CureLight lamp, is indicated for the treatment of non-hyperkeratotic actinic keratoses. Topical application of methyl aminolevulinate results in formation of photoactive porphyrins, which are localized specifically in pre-malignant and malignant tumors of epithelial origin. When photoactive porphyrins are exposed to light of an appropriate wavelength in the presence of oxygen, a photochemical reaction takes place. This results in the production of singlet oxygen, which destroys intracellular components, in particular the mitochondria, leading to cell death. The activation of photosensitizers with resultant cytotoxicity forms the basis of photodynamic therapy of pre-malignant or malignant cells. Thus, application of Metvix cream to actinic (solar) keratoses causes photosensitization confined to the target lesions. Subsequent illumination of lesions leads to destruction of target lesions without risk to surrounding normal skin.

Photodynamic therapy for actinic keratoses with Metvix cream is a two-stage process involving (1) superficial preparation of the lesions followed by application of Metvix cream to target lesions for 3 hours under occlusive dressing, and (2) removal of the dressing and rinsing off excess cream followed by illumination with red light of wavelength 570 to 670 nm and total light dose of 75J/cm², using a "CureLight lamp." Metvix cream is not intended for any device other than the CureLight lamp. Metvix cream will be available in 2 g tubes containing 168 mg of methyl aminolevulinate per gram.

II. RISK ASSESSMENT:

Metvix cream is not intended for application by patients; only trained practitioners are intended to administer Metvix. Therefore, OPDRA did not perform prescription analysis studies.

The medication error staff of OPDRA did however, conduct a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound like or look like "Metvix" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. Additionally, an expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Metvix. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified two proprietary names, Mavik and Mentax, that were thought to have the potential for confusion with Metvix. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K. (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

⁴ The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1>

⁶ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Metvix	Methyl Aminolevulinate Cream 168 mg/g 2 g tube	To be applied by trained personnel only. STEP A – Lesion should be debrided to remove scales and crusts and roughen the lesion surface. Apply a layer of Metvix cream about 1 mm thick to the lesion and surrounding skin. Cover with occlusive dressing for 3 hours. STEP B – Remove the dressing, clean the area with saline and gauze. Immediately expose the lesion to red light with a continuous spectrum of 570 to 870 nm and a total light dose of 75J/cm ² . Metvix cream is intended for use with only a "CureLight" lamp.	
Mavik	Trandolapril Tablets 1 mg; 2 mg; 4 mg	1-4 mg by mouth once daily.	S/A and L/A per OPDRA
Mentax	Butenafine HCL Cream 1% 15 g tube; 30 g tube	Interdigital tinea pedis: apply twice daily for 7 days, or once daily for 4 weeks; Tinea Corporis or tinea cruris: apply once daily for 2 weeks.	S/A and L/A per OPDRA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Metvix, the primary concern raised by the expert panel was related to two potential sound-like/look-alike names, Mavik and Mentax.

Mavik is the proprietary name for Trandolapril, an angiotensin-converting enzyme (ACE) inhibitor, used as monotherapy or in combination with drugs from other classes of antihypertensive agents. Mavik is marketed as 1 mg, 2 mg, and 4 mg oral tablets. The usual daily dose is 1-4 mg, given as a single daily dose. Both Mavik and Metvix are two syllable words that begin with the letter "M." When written by prescription in clinical settings, there is a risk that the two names will appear similar. In addition, because both Metvix and Mavik begin their second syllable the letter "v," there is a risk that the interpretation of verbal prescriptions will sound alike. However, due to the differences in dosage form, tablet vs. cream, route of administration, oral vs. topical, dosage and frequency of dosing, OPDRA has reduced concerns that Mavik would be used in error with Metvix.

Mentax is the proprietary name for butenafine HCl cream 1%. Butenafine HCl is a synthetic anti-fungal agent, and a member of the class of anti-fungal compounds known as benzylamines. Mentax cream is indicated for the topical treatment of the following superficial dermatophytoses: interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch), due to *E. floccosum*, *T. mentagrophytes*, *T. rubrum*, and *T. tonsurans*.

Both Metvix and Mentax are two syllable words that begin with the letter “M” and end with the letter “x.” These facts pose the risk that Metvix and Mentax could appear similar on a written prescription. In addition, there is risk that the two names will sound alike in verbal prescriptions. Furthermore, both Metvix and Mentax are creams for dermatological conditions. Mentax is administered either twice daily for 7 days, or once daily for 4 weeks depending on the indication of use. Although Mentax and Metvix share a similar dosage form and route of administration, the directions for use, conditions and settings in which it the products are used, are markedly different.

Metvix is intended for use only by trained personnel in highly controlled settings. The Dosage and Administration for Metvix is a complicated two step process that necessitates patient monitoring by trained personnel. The package insert labeling “Information for Patients” section, clearly instructs patients that Metvix is to be applied by a trained practitioner only. The patient is further instructed that they will be given eye protection goggles to wear during red light treatment of their lesions treated by the cream. Given the controlled supervised setting in which Metvix will be used, the risk of Metvix and Mentax being used in error is reduced.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

OPDRA reviewed the proposed container label, carton and package insert labeling, and have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. Container Label (2 g)

1. Include the product strength.
2. If space permits, include “For Topical Use.”
3. The established name should be revised to include the finished dosage form “cream.”

B. Carton Labeling (1 x 2 g)

1. The established name should be revised to include the finished dosage form “cream.”
2. We note you express the product strength as 168 mg/g cream. The strengths of creams are generally expressed as a percentage. We recommend revising the expression of the strength accordingly.
3. Relocate the route of administration to appear prominently on the main panel and revise to read “For Topical Use.”
4. We recommend including a statement ‘ _____ to minimize the risk that the product be used other than as intended.

C. Package Insert

1. Precautions

To be in accordance with 21 CFR 201.57 (f)(z) the full text of the information for patients

section should be reprinted at the end of the labeling.

2. Dosage and Administration

The statement "This product is not intended for application by patients or unqualified medical personnel," appears as the 4th paragraph under Dosage and Administration. The statement "Metvix cream is not intended for any device other than the CureLight lamp," appears in the 10th and last paragraph. To ensure Package Insert readers understand the importance of these two safety statements, OPDRA recommends that

IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name Metvix.
2. OPDRA recommends implementation of the container label and carton and package insert labeling revisions outlined in Section III of this review to minimize the potential misuse of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have further questions or need clarifications, please contact Kevin Dermanoski at 301-827-6277.

Kevin Dermanoski, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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

/s/

Kevin Dermanoski
1/2/02 10:37:59 AM
CSO

Jerry Phillips
1/2/02 10:51:32 AM
DIRECTOR



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 12-19-01

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject: Request for information for NDA 21-415

Total no. of pages including cover: 2

Comments: Please see following page(s). If you have any question, please call me.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-415
METVIX

*Case is
1-24-01
Paxel
preparation*

Request for information:

Will you please provide the following information and when you expect to submit the amendment to the NDA. Send me a fax with this information, please. We will need two copies- one archival and one reviewer copy. If there is information for more than one reviewer, please submit three official copies. If you have questions as to how many copies to send, give me a call.

- The exact study dates (first patient treated and last patient follow-up) for Study PC T305/99. The study dates provided were March 2000 to December 2000.

-Need investigator name with the associated center # and location for each of the 9 centers for Study PC T305/99.

-Where in the submission are the credentials located for Dr. Weightman (Protocol PC T305/99)?

-Please provide case report forms (including photographs) for the following patients (Study PC T305/99):

- nos. 1021 & 6012
- no. 3008
- no. 1003
- no. 3014
- nos. 3016 & 3026

CLEMENTI
& Associates

RECEIVED

December 19, 2001

DEC 26 2001

VIA FACSIMILE AND FEDEX

MEGA/CDER

ORIGINAL

BS
NDA 21-415 SUPPLEMENT

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

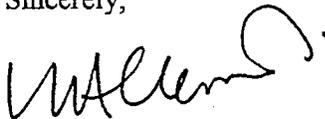
Re: ANSWERS TO FDA QUESTIONS FOR NDA 21-415

Dear Ms Lutwak:

In response to FDA question of November 29, 2001, Items I and J contain appendices that were not provided in the original NDA 21-415 submission. These appendices reflect the current data available for the questions received from the Division, Biostatistics Team.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files
FDA Form 356h (No: 8)

CLEMENTI
& Associates

RECEIVED

December 19, 2001

VIA FACSIMILE AND FEDEX

JAN 25 2002

MEGA/CDER

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: ANSWERS TO FDA QUESTIONS FOR NDA 21-415

Dear Ms Lutwak:

Responses to FDA's questions of December 19, 2001 are provided for your information and review. Each of the questions is answered by supporting data including case report forms and photographs. A copy of the list of questions sent by the Division is appended for ease of review. The supporting data is ordered according to the list of FDA's questions.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

FDA Form 356h (No: 10)

ORIGINAL

NC

FW CORRESPONDENT

CLEMENTI
& Associates

RECEIVED
DEC 14 2001
MEGA/CDER

December 12, 2001

VIA FACSIMILE AND FEDEX

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: ANSWERS TO FDA QUESTIONS FOR NDA 21-415

Dear Ms Lutwak:

In order to expedite our response, PhotoCure ASA is providing a partial set of answers to questions received from the FDA on November 26, 2001 (Items A -E) and November 29, 2001 (Items F-H). The information provided explains PhotoCure's position on each of the questions and provides information pertaining to each item. The answers to the questions for Items J and K on November 29, 2001, will be provided separately as soon as the Appendix Tables are received. This is a initial response.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files
FDA Form 356h (No: 7)

ORIGINAL



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 11-29-01 - *Refaxed 2-6-02* *Fax 11-26-01* *Fax 11-29-01* *+ additional request VL*

To: William Clementi, Pharm.D.	From: Victoria Lutwak
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject:
 Request for information for NDA 21-415
 I would like to know when this information will be available. Please let me know your proposed timeline for submission for these request from the statistician and biopharm reviewers and for the previous request from the medical officer. We would like the protocol on diskette as soon as possible. If you have any question, please call. Thank you. *Vickey*

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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NDA 21-415
METVIX

REQUEST FOR INFORMATION:

BIostatistics Comments: To facilitate statistical review of NDA 21-415, this reviewer requests the Sponsor to submit the following items:

*Scanning
request to*

H

Provide detailed description about randomization/blinding procedure for study PC T305. Please clarify the difference between three columns in your randomization list (i.e. columns of "treatment", "investigators envelop", and "randomized to" in Volume 47 of the NDA).

- I. As commented by the Agency at the End-of-Phase 2 and Pre-NDA meetings (i.e. 6/22/00 and 5/2/01), one-sided 97.5% confidence interval should be used for non-inferiority evaluation. Please provide both ITT and PP analyses based on one-sided 97.5% confidence interval for the difference between Metvix and cryotherapy with respect to patient excellent response rate and weighted patient response rate for study PC T305.
- J. Provide subgroup efficacy results by age and gender for each of studies PC T305, 302 and 301 with respect to the primary and secondary efficacy endpoints.

NDA 21-415
METVIX

11-29-01

REQUEST FOR INFORMATION

Biopharm Request:

going well check

- Please provide a full report on the development and validation of fluorescence measurement methodology. ←
- In-vitro release study (Optional, but it may be helpful for the sponsor in future for SUPAC related issues).

8-19-02 - VL. asked Dr. C. - if they were reading in a response tomorrow, why the question now? They have had the fax since 11-29-01 - why 2 months later?

2-19-02 E. Dr. Bashaw

PP 9 — classification internal standards prep & validation -



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 11-26-01

To: William Clementi, Pharm.D.	From: Victoria Lutwak <i>VL</i>
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073

Subject: Request for information for NDA 21-415

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-415
METVIX

Request for information:

According to the Pre-NDA meeting minutes we requested the following:

"...The Agency request the Sponsor to submit Word 97 files for text and in-text tables for the following sections:

1. Protocol and proposed label—*We have a PI but no container and carton e-file.*

Please send these. VL

yes yes
- L 2-19-02 - have only send PDF
not word files.

gens
agmt

2. Application Summary

3. Clinical Data Section

4. Clinical Study Reports

5. ISE and ISS— *This is on the CD correct? VL*

In addition, please send the following:

gens

1. The Sponsor should provide site-breakdown of the data from the two pivotal multicenter studies.... Did the Sponsor submit any of the above? — 32599 - come in - check file 15 DEC 19

2. An electronic copy of the protocol. — *have a copy*

3. Also, a video-training program to standardize the preparation of lesions was noted in the Pre-IND Meeting minutes (pg. 4) held June 22, 2000. Was a video-training program used for investigators conducting the clinical trials? If so, please provide a copy.

agmt

4. (Vol. 1.1, pg. 158, Foreign Marketing) The Sponsor lists a Mutual Recognition Procedure, "Day 0" for European countries. Please provide a brief explanation. — *Victory*

BC

November 14, 2001

CLEMENTI

Associates

Jonathan Wilkin M.D.
Director,
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research
HFD 540
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RECEIVED

NOV 16 2001

MEGA/CDER

**RE: New Drug Application 21-415
Metvix 168 mg/g Cream (methyl aminolevulinate)**

Dear Dr. Wilkin:

Enclosed please find revised volumes 2 through 7 for NDA 21-415 (Item 4 Chemistry, Manufacturing and Controls). The revisions are submitted as follow-up to a telephone conference between Division chemist Dr. James Vidra and Dr. William Clementi on November 6, 2001, and fulfill our commitment to supply the revisions within one working week. During the conversation Dr. Vidra requested organizational changes and revisions in the Table of Contents in order to facilitate the location of information and thereby facilitate his review of the CMC section of the NDA. The requested changes relate mainly to the Table of Contents section of the volumes containing Item 4, and to the identification of some of the tabs in each section. In response to Dr. Vidra's requests, we have made the following changes in the CMC volumes:

- Each volume of the CMC section (Item 4) contains its own Table of Contents, which is located at the beginning of the volume. The volume Table of Contents is detailed to the fifth level of headings e.g. 4A.8.4.4 "Assay by High Pressure Liquid Chromatography" etc.
- Appendices and Attachments are identified within each Item.
- Tabs have been added for Appendices (and for Attachments in the Drug Section).
- The Item numbers have been added to the heading titles for all tabs.
- Throughout the CMC section when Items are referred to in the text, the Volume numbers are stated if the Items are located in a different Volume. If the items are located in the same Volume, the Volume number is not stated.

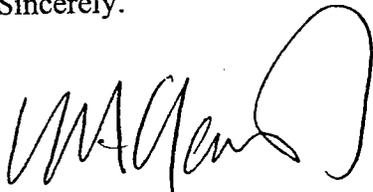
ORIGINAL

- When referencing Appendices and Attachments, the Item identification is stated unless the Appendix or Attachment is located in that same Item. In these instances no Item identification is stated.
- The Table of Contents for the Method Validation Package is provided in Item 4E Volume 7 (page 148).
- The lot numbers for the samples identified in the Methods Validation Package have been provided under Item 4D Samples.
- Pages that have been changed are identified in the footer with the notation "Revised date: November 14, 2001". However, please note that the changes made are organizational changes noted above e.g. new Table of Contents pages, cross-references etc. There have been no changes in wording or scientific content or conclusions in any of these volumes.

Also, please note that the GMP compliance certification for the Drug Substance is located in Volume 2 (page 68).

We hope these changes facilitate navigating through the CMC volumes and thereby facilitate the CMC review of NDA 21-415. If you or Dr. Vidra require any additional information or have any further questions please do not hesitate to contact me.

Sincerely,



William A. Clementi, Pharm.D. F.C.P.
President
Clementi & Associates, LTD.

US Agent, PhotoCure ASA

Copy: Regulatory files, US and Norway



N-000/BC
NDA ORIG AMENDMENT

November 13, 2001

VIA FEDEX

RECEIVED

NOV 14 2001

MEGA/CDER

Ms. Kalyani Bhatt
Project Manager
Center for Drug Evaluation and Research
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: Methods Validation Package for NDA 21-415

Dear Ms Bhatt:

Enclosed are three (3) copies of the Methods Validation Package for NDA 21-415.

This package has been updated to provide quicker and easier cross-referencing between different areas of the NDA. An updated, more informative Table of Contents has also been provided, with the pages of the Methods Validation Package being renumbered in accordance with FDA requirements. Each appendix has been identified, tabbed and updated as per your verbal request. This fulfills our verbal commitment of November 6, 2001.

If you have any questions or require any additional information, please contact me at (610-581-7021).

Sincerely,

William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

ORIGINAL



NOV - 9 2001

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

PhotoCure ASA
c/o Dr. William A. Clementi, F.C.P.
Clementi & Associates
919 Conestoga Road
Rosemont, Pennsylvania 19010

Re: P010061
CureLight BroadBand Model CureLight 01
Filed: September 27, 2001

Dear Dr. Clementi:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is September 27, 2001, which is the date of CDRH receipt of the PMA.

This letter reflects the current progress of our administrative and limited scientific review of your application. Please be advised that the decision to file the PMA does not imply that either an in-depth evaluation of the safety and effectiveness of the device has been performed or a decision about the approvability of the application has been made. Rather, it represents a decision by CDRH that the application is sufficiently complete to begin the substantive review process. Further review of your application may result in deficiencies, which will be communicated to you.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit clinical updates in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

Page 2 - Dr. William A. Clementi, F.C.P.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with the conditions set forth in your application and the applicable requirements of the Quality System Regulation (21 CFR Part 820). If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301)-594-4695, or your District Office.

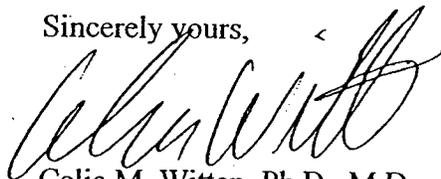
Should CDRH schedule this PMA for review at a public meeting of the General and Plastic Surgery Advisory Panel, you will be notified of the location and date of this meeting. If such a decision is made, it is probable that such a meeting would be a combination meeting with the corresponding Advisory Panel from the Center for Drug Evaluation and Research.

All correspondence regarding this PMA should be submitted in triplicate copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions regarding this letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours,



Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

November 8, 2001

Review of P010061

Submitted by Clementi & Associates
for PhotoCure ASA

Reviewed by Richard P. Felten, DGRND, GSDB

This PMA was submitted as part of a drug/device combination application, NDA 21-415. The PMA consists of those volumes of the NDA submitted to CDER for the approval of a new drug called Metvix 168 mg/g Cream (methyl aminolevulinate) for the treatment of actinic keratosis. The device which is the subject of the PMA has the trade name CureLight BroadBand and is used to activate Protoporphyrin IX (PpIX) in the target lesions. This system produces lesion clearance by the application of the Metvix Cream to the lesion and 3 hours after application applying red light (570-650 nm) produced by the CureLight. The Metvix cream is absorbed into the lesion and produces an increase in the amount of PpIX present in the lesion. PpIX is a photosensitizer and is activated by red light producing single oxygen, which produces cell death.

This review was limited to an administrative review to insure that all necessary information has been provided. A more detailed review is necessary to identify any deficiencies.

Note, since this PMA is part of a combination drug/device system with CDER lead, final decisions by CDER on indications for use wording and possible labeling in terms of patient information will affect the final labeling for the device.

CDER did meet on November 7, 2001 and a decision was made at the meeting that the NDA was filable. Under CDER review, the NDA does not need to be filed until 60 days after receipt, that is by November 26, 2001 and the actual review clock for this filing is 10 months. I did point out to CDER that we would be filing the PMA as of Friday, November 9, 2001 and would probably be sending an Approvable letter by end of January to meet our PMA review clock of 180 days and still have time at the end to clarify labeling based on the NDA approval.

The CureLight system is a halogen lamp contained in a housing with a cooling fan to keep the lamp from over heating. The light pathway passes through 2 IR filters to remove wavelengths above 650 nm and also to remove heat. The light passes through a glass rod and a aspheric focusing lens. The device comes with a light monitoring probe which is used to establish the correct dose to the target site. The lamp is capable of treating spot sizes from 35-50 mm and this is obtained by raising and lower the lamp housing to alter spot size. The directions for use clearly warn for the need for both physician and patient to wear protective eyewear during treatment.

Treatment fluence has been established as 75 J/cm^2 with the dose rate being between 50 and 200 mW/cm^2 . There is a calibration step using the light monitoring probe which automatically calculates the dose rate based on spot size and the required fluence.

The information provided in the PMA does include all of the required elements to allow for a substantive review. Since CDER has lead for the NDA, there is no need for statistical or labeling review by CDRH. Manufacturing volumes will be reviewed by Office of Compliance and CDRH will perform the inspection for the device manufacturing site.

I recommend that this application be filed.

CLEMENTI
& Associates

RECEIVED
NOV 07 2001
MEGA/CDER

November 6, 2001

VIA FACSIMILE & FEDEX

NC
NEW CORRESP

ORIGINAL

Ms. Kalyani Bhatt
Project Manager
Center for Drug Evaluation and Research
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: Methods Validation Package for NDA 21-415

Dear Ms Bhatt:

In response to your recent request for a Methods Validation Package for NDA 21-415, we are now in the process of compiling the documentation. The compilation will require five (5) working days starting November 7, 2001. Therefore, we commit to having the Methods Validation Package for NDA 21-415 to you no later than November 14, 2001.

If you have any questions or require any additional information, please contact me at (610-581-7021).

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd*

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files



October 30, 2001

VIA FEDEX

Ms. Kalyani Bhatt
Project Manager
Center for Drug Evaluation and Research
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: NDA 21-415 (Metvix[®] Cream)

In response to the question raised by Dr. James Vidra (Chemistry Reviewer), neither the _____
_____ have CFN numbers.

If you have any questions or require any further information, please telephone Clementi & Associates Ltd at (610) 581-7021.

Sincerely,

A handwritten signature in black ink, appearing to read 'William Clementi', with a large, stylized circular flourish at the end.

William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

REQUEST FOR CONSULTATION

vision/Office): **Richard Felten**

FROM: DDDDP (Division of Dermatologic and Dental Drug Products) HFD-540
Kalyani Bhatt, Project Manger

IND #: 10-22-01	IND #:	NDA #: 21-415	TYPE OF DOCUMENT :	DATE OF DOCUMENT: 9-27-01
-----------------	--------	---------------	--------------------	---------------------------

NAME OF DRUG: Metvix Cream	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE:
----------------------------	-------------------------	----------------------------	--------------------------

NAME OF FIRM:

REASION FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | New NDA Submission |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): New NDA Submission

III. BIOPHARMACEUTICS

- | | |
|---|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISION RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS:

SIGNATURE OF REQUESTER Kalyani Bhatt, Project Manager DDDDP, HFD-540 301-827-2049	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> Electronic & Internal MAIL <input type="checkbox"/> HAND
---	---

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
-----------------------	------------------------

NDA ORIG AMENDMENT

BL

CLEMENTI
& Associates

June 11, 2001

VIA FEDEX

RECEIVED
JUN 12 2002
MEGA/CDER

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

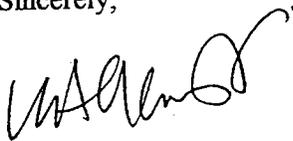
Re: Camera Ready Carton and Tube Labels - Metvix[®] Cream (NDA 21-415)

Dear Ms Lutwak:

In response to the FDA's request we are providing the drawings for Metvix 160 mg/g cream carton and tube labels in camera ready format.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

FDA Form 356h (No: 36)

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): OPDRA HFD - 400 Sammie Beam			FROM: KALYANI BHATT, REGULATORY PROJECT MANAGER DDDDP, HFD-540 301-827-2049		
DATE 10-22-01	IND NO. 59,756	NDA NO. 21-415	TYPE OF DOCUMENT Consult for Tradename	DATE OF DOCUMENT September 27, 2001	
NAME OF DRUG Metvix Cream 168 mg/g		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Keratolytics	DESIRED COMPLETION DATE	
NAME OF FIRM: Photocure ASA					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA SUBMISSION	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:					
SIGNATURE OF REQUESTER KALYANI BHATT PROJECT MANAGER HFD-540 301-827-2049			METHOD OF DELIVERY (Check one) <input type="checkbox"/> X MAIL <input type="checkbox"/> X HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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

/s/

Kalyani Bhatt
10/22/01 02:02:27 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(L 15B-03, PKLN Bldg.)

FROM:
Vickey Lutwak, Project Manager

DATE April 23, 2002	IND NO. 59,756	NDA NO. NDA 21-415	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT September 27, 2001
NAME OF DRUG METVIX		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Keratolytics	DESIRED COMPLETION DATE ASAP if objections with the tradename PDUFA date JULY 24, 2002

NAME OF FIRM: Clementi & Associates U.S. Agents for PhotoCure ASA, Norway

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: The TRADENAME was reviewed Dec. 24,2001, by OPDRA Consult # 01-0218 . At that time OPDRA had no objections to the proprietary name Metvix. But we have we have new concerns with the Metvix name in relation to what we learned from the sponsor regarding their plans for distribution. There may be a potential for a drug mix-up. Please review the following:
If it is distributed in the pharmacy, the potential drug mix-up is a real issue with Mentax. When we talked to the sponsor recently about distribution, he could not guarantee that Metvix will never be distributed by a pharmacy. Neither could he guarantee that the drug would only be distributed in the physician's office.
This may not be a safety issue as much as an efficacy issue. The chemist stated that the drug product is stable for _____ at room temperature. This could be an issue if the products are confused-- Metvix and Mentax-- and Metvix is put on the shelf rather than in the refrigerator. Can a product be approved for distribution limited to a physician's office only? This would eliminate the potential for mix-ups.
I would please review this new information as well as the tradename. Thank you.

SIGNATURE OF REQUESTER Vickey Lutwak	METHOD OF DELIVERY (Check one) DFS <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED

APPLICANT INFORMATION

NAME OF APPLICANT
Photocure ASA

DATE OF SUBMISSION
September 27, 2001

SEP 26 2001

TELEPHONE NO. (Include Area Code)
722062213

FACSIMILE (FAX) Number (Include Area Code)
4722062218

CDR/CDER

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
Photocure ASA
Kjellerveien 48
N-0377, Oslo
Norway

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
Dr. William A. Clementi, Pharm.D., F.C.P.
Clementi & Associates
919 Conestoga Road
Rosemont, PA 19010
Phone: 610-581-7021
Fax: 610-581-7025

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Methyl aminolevulinate hydrochloride

PROPRIETARY NAME (trade name) IF ANY Metvix

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any) P-1202

DOSE FORM: Cream

STRENGTHS: 168mg/g

ROUTE OF ADMINISTRATION: Topical

PROPOSED INDICATION(S) FOR USE: non-hyperkeratotic actinic keratoses

APPLICATION INFORMATION

APPLICATION TYPE

(Check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

68

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name,
address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing)
conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached for full listing of information

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Photocure IND 59.756

DMF

DMF

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SEP 27 2001

PAGE 1

FORM FDA 356h (4/00)

MES/COE

ORIGINAL



RECEIVED

September 27, 2001

OCT 04 2001

MEGA/CDER

Jonathan Wilkin, M.D.
Director,
Division of Dental and Dermatological Drug Products
Center for Drug Evaluation and Research
HFD 540
Food and Drug Administration
9201 Corporate Blvd.
Rockville MD 20850

RECEIVED

SEP 26 2001

CDR/CDER

10/29/01

side

- CFN # from FOA?
- cannot find # or set up inspection

RE: New Drug Application 21-415
Metvix 168 mg/g Cream (methyl aminolevulinate)

Dear Dr. Wilkin:

We are submitting, herewith, a completed application to market a new drug for human use (form FDA 356h), for Metvix 168 mg/g Cream (methyl aminolevulinate) in combination with CureLight. The drug-device combination [Metvix Cream and CureLight used in combination constitute Photo Dynamic Therapy (PDT)] is intended for the treatment of actinic keratosis. This submission is comprised of a review copy and an archival copy as required by 314.50 (h) and, in addition, as requested by Richard Felton one copy for review by the Center for Devices and Radiological Health. Electronic versions of Items 1, 2, 11, and 12 are provided for ease of review and in accord with discussions with R. Levin and K. Bhatt. Accordingly, no paper copy of Item 11 is provided, but will be submitted upon request. Item 2 is provided in pdf and Word format. In addition, Items 8G, 8H and 8J, Integrated Summaries of Effectiveness, Safety, and Benefits and Risks, are also provided electronically in the pdf format; Items 8G and 8H also in Word format. Fifteen copies of Volume 1.1 are provided as requested by K. Bhatt on 9/18/2001. Metvix 168 mg/g Cream was investigated in clinical studies in actinic keratosis in Europe, and in the United States under IND 59,756.

Non-U.S. Studies

The studies reported here that were conducted outside the United States are used in support of this NDA because they were conducted in accordance with Good Clinical Practice and meet the FDA requirement for acceptance. The following documentation for these non-US studies is contained in Item 8 Clinical Data:

- Description of investigators qualifications
- Detailed summary of the protocol(s) and results of the studies.
- If requested by FDA, PhotoCure will provide case records maintained by the investigator or additional background data such as hospital or other institutional records

- A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications and bioavailability of the specific drug product used in the clinical study.
- Statement of conformance with ethical principles stated in the Declaration of Helsinki.
- Explanation of how each study conformed to the principles of the Declaration of Helsinki, or the host country's standards.
- Documentation of independent review committee review and approval, and names and qualifications of committee members

Pediatric Studies

On August 8, 2000 PhotoCure requested a full waiver of the requirements to conduct clinical studies with Metvix 168 mg/g Cream in pediatric populations in accordance with 21 CFR 314.55. That request was based on the fact that Metvix 168 mg/g Cream does not represent a meaningful therapeutic benefit over existing treatments modalities for pediatric patients. Consequently it is not likely to be used in substantial numbers of pediatric patients because of the rare rate of occurrence of actinic keratosis in children, and the high success rate in these patients with available treatment modalities. PhotoCure is again requesting this waiver, and the request is provided in Item 1.

Phototoxicity Studies

On August 14, 2000 PhotoCure requested that the Division grant a waiver of all requirements to conduct phototoxicity studies with Metvix 168 mg/g Cream. This request was based on the fact that Metvix Cream exerts its therapeutic effect in the treatment of actinic keratosis by inducing the formation of the known photosensitizer to AK. PhotoCure is again requesting this waiver, and the request is provided in Item 1.

Waiver of Application Fees

On March 7, 2001, in a letter to Ms. Jane Axelrad, CDER Associate Director for Policy, PhotoCure formally requested a waiver of the Application fees for this New Drug Application in accordance with Section 736 (d)(1)(E) of the Federal Food Drug and Cosmetic Act. This New Drug Application qualifies for the waiver of fees under Section 736 because PhotoCure is a small business with fewer than 500 employees and this is our first New Drug Application ever submitted to the Food and Drug Administration. The Food and Drug Administration granted our request for the waiver of application fees in a letter dated August 1, 2001. A copy of that letter is included in Item 1.

CureLight

Metvix PDT includes illumination with the CureLight lamp of the areas of skin to which Metvix 168 mg/g Cream has been applied. Information on the CureLight lamp is included in Item 21. The device information is contained in a separate Item and follows the format specified in FDA's Guidance on Pre-Market Approval for a New Device.

Pre-Approval Inspection

All facilities will be ready for FDA inspection by February 2002.

Chg'd. to 11-15-01.

Pre-NDA Meeting

This NDA was discussed with the division during a pre-NDA meeting between representatives of the Division and PhotoCure, held May 2, 2001. On May 30, 2001, as a follow-up, PhotoCure provided the Division with minutes of that meeting reflecting PhotoCure's understanding of the Pre-NDA meeting, and subsequently PhotoCure received FDA's version. FDA's memorandum is included in Item 20, along with a copy of the Division's minutes of the Pre-NDA meeting and PhotoCure's response to issues. We believe that PhotoCure has met all of the recommendations made by the Division.

Labeled Amount of Metvix Cream

Reports contained in Items 5, 6 and 8 refer to Metvix Cream. The labeled amount was revised to 168 mg/g. Please refer to Item 4.B.3 for complete details.

Studies satisfying requirements for safety and efficacy

Data from 4 well-controlled Phase III clinical studies with Metvix 168 mg/g Cream in patients with actinic keratosis is included in this NDA submission. Three of the studies were placebo-controlled and 2 used an active control (cryotherapy). Safety and efficacy data has been collected from altogether 2239 patients. In the Phase III studies in actinic keratosis, 520 patients were treated; 251 with Metvix 168 mg/g Cream, 80 with placebo and 189 with cryotherapy. Also, 139 patients received Metvix Cream during Phase II dose ranging and subtle pharmacology studies.

A brief review of actinic keratosis, its diagnosis, prognosis, and treatment is included as part of Item 3B. Also included in Item 3B is a discussion of the scientific rationale, method of treatment, and clinical benefits of Metvix 168 mg/g Cream.

NDA Organization

The Metvix 168 mg/g Cream New Drug Application is organized according to the format described in form FDA 356h and consists of 68 volumes. Volume 1.1 contains the completed application form, patent information, Drug Master File (DMF) letters of authorization, certification as per 306 (k)(1), the overall table of contents, product labeling and the overall (Item 3) summary. The Item 3 summary follows the guidelines for the Format and Content of the Summary for NDA and Antibiotic Applications.

The NDA location references shown in the overall table of contents and within summary tables are to the NDA page numbers.

As per the guidelines on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications, each review section (Chemistry, Human Pharmacokinetics and Bioavailability, Clinical, and Statistical) is provided with a copy of Volume 1.1. Each review section (Items 4 through 10) and subparts is provided with a relevant table of contents and list of tables and figures. If an Item or report occupies more than one volume, the Item or report table of contents is contained in each of those volumes.

Throughout the NDA, studies are referenced by their respective report number. Reports that are applicable to more than one Item (e.g. pharmacodynamic studies Item 6 and Item 8) are provided in their entirety within the Item. Similarly, Item 10 Statistical section contains, in addition to a brief introductory summary of statistical methods used, the identical information as provided in Item 8 Clinical data section.

The technical summary sections are organized as follows:

Volume	Section
1.2-1.7	Chemistry (CMC) (Item 4) The CMC documentation for the drug product is provided in Volumes 1.2 - 1.7. The Environmental Assessment is contained in Volume 1.7. The Methods Validation package is contained in a separate, appropriately labeled Volume. Product samples are not included in this application but will be submitted upon request by the agency. The proposed prescribing information for Metvix 168 mg/g Cream is provided along with the draft immediate container labels for the tube in Item 2 Draft Labeling , Volume 1.1.
1.8-1.14	Nonclinical Pharmacology and Toxicology (Item 5) Nonclinical studies are contained in Volumes 1.8 – 1.14. Draft reports and final reports submitted to the IND did not differ substantially, and highlighting of differences was not warranted.
1.15-1.20	Human Pharmacokinetics and Bioavailability (Item 6) Data describing the human pharmacokinetics and bioavailability of methyl 5 – aminolevulinate after topical application are summarized in Volume 1.15. Individual study reports are contained in Volumes 1.15 - 1.20. It is not possible to provide reports electronically at this time, however reports can be provided electronically during the review.
1.21-1.40	Clinical Data (Item 8) This application contains analysis of data from 17 clinical studies including totally 2239 subjects, comprised in the safety population. An open-label, compassionate use study included 1012 patients. In the remaining 16 clinical studies, 652 patients with actinic keratosis and 477 patients with basal cell carcinoma were treated. In the Phase III studies in actinic keratosis, totally 520 patients were included; 251 received Metvix Cream, 80 received placebo and 189 had cryotherapy. The Integrated Summary of Efficacy (ISE) is located in Volume 1.36, with the Integrated Summary of Safety (ISS) in Volume 1.37. Principal trials and Clinical Pharmacology Individual Study Reports are contained in Volumes 1.21 – 1.35.
1.41-1.60	Statistical (Item 10)

- 1.61 Case Report Tabulations (Item 11)**
Case report form tabulations are provided for the principal trials only, and only in electronic format (Volume 1.61). The Clinical, Statistical and Device review sections have been provided with copies of these tabulations.
- 1.62-1.65 Case Report Forms (Item 12)**
The Case Report Forms for patients who died, experienced serious adverse events or were withdrawn for adverse events are contained in Volumes 1.62 - 1.65. Deaths occurred in studies 202/98, 206/98, 301/99 and 304/99. Serious adverse events and withdrawals for adverse events both occurred in studies 202/98, 203/98, 204/98, 301/98, 304/98, 305/98 and 306/98.
- 1.1 Patent Information (Item 13)**
A US patent has been granted for use of Metvix 168 mg/g Cream. A full statement regarding the patent is contained in Volume 1.1 in accordance with 21 USC 355(b) or (c).
- 1.1 Patent Certification (Item 14)**
To our knowledge there are no patents (except PhotoCure's patent) in effect for Metvix 168 mg/g Cream. In accordance with 21 USC 355 (b)(2) or (j)(2)(A), a PhotoCure certification to this effect is contained in Volume 1.1.
- N/A Establishment Description (Item 15)**
Not applicable
- 1.1 Debarment Certification (Item 16)**
No investigators debarred by FDA from conducting studies to be used in support of New Drug Applications have been included in the Metvix development program. In accordance with Section 306 (k)(1) of the Food Drug and Cosmetic Act, a certification to this effect is contained in Volume 1.1
- 1.1 Field Copy certification (Item 17)**
In accordance with 21 CFR 314.50 (k)(3) a copy of the CMC section of this application (Item 4) is being sent to the FDA Field Office at Philadelphia, PA. The certification by PhotoCure to this effect is contained in Volume 1.1.
- 1.1 User Fee Cover Sheet (Item 18)**
The User Fee Cover sheet is contained in Volume 1.1
- 1.1 Financial Information (Item 19)**
Financial information required by 21 CFR Part 54 is included in Volume 1.1.
- 1.66-1.68 Device (Item 21)**
The device information for CureLight follows the format specified in FDA's Guidance on Pre-Market Approval (PMA) for a New Device.

Overall we believe that the data presented in this New Drug Application demonstrate the safety and efficacy Metvix cream 168 mg/g (methyl aminolevulinate) and the CureLight PDT when applied topically for the treatment of actinic keratosis. We would welcome any opportunity to discuss in general, or in detail, any aspect of this application.

Please feel free to contact me at (610) 581-7021

Sincerely

A handwritten signature in black ink, appearing to read 'WAClementi', written in a cursive style.

William A. Clementi Pharm.D. F.C.P.
President
Clementi & Associates Ltd

US Agent, PhotoCure ASA

Copy: Regulatory files, US and Norway

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

PhotoCure ASA
Hoffsveien 48
N-0377 Oslo
Norway

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-415

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(011) + 47 22 06 22 10

3. PRODUCT NAME

Metvix® cream

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

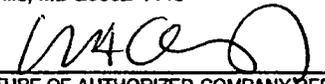
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE


William A. Clementi Pharm.D. F.C.P.

TITLE

President,
Clementi & Associates, Ltd

DATE

September 18, 2001



AUG 1 2001

Food and Drug Administration
Rockville MD 20857

Dr. William Clementi
Clementi & Associates, Ltd.
919 Conestoga Road
Rosemont, PA 19010

**RE: PhotoCure ASA, Small Business Application Waiver Request 2001.028,
Metvix Cream**

Dear Dr. Clementi:

This responds to your request of March 26, 2001, on behalf of PhotoCure ASA (PhotoCure), for a waiver of the human drug application fee for the new drug application (NDA) Metvix (methyl 5-aminolevulinate) 168 mg/gram cream, under the small business waiver provision of section 736(d)(1)(E)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2001.028). For the reasons described below, the Food and Drug Administration (FDA) grants the request from PhotoCure for a small business waiver of the application fee.

According to your waiver request, PhotoCure is a small business with — employees and no affiliates or parent company. You state that PhotoCure is applying for the application fee waiver for the first human drug application submitted to FDA by PhotoCure.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate² submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant a small business waiver to PhotoCure is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated July 2, 2001, that PhotoCure has fewer than 500 employees, including those of its affiliates, PCI Biotech AS and PhotoCure Australia Pty. Ltd. Second, according to FDA records, the marketing application for PhotoCure's Metvix (methyl 5-aminolevulinate) 168 mg/gram cream will be the

¹ 21 U.S.C. 379h(d)(1)(E).

² "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

first human drug application, within the meaning of the Act, to be submitted to FDA by PhotoCure or its affiliates. Consequently, your request for a small business waiver of the application fee for Metvix cream is granted.

FDA records show that PhotoCure's NDA has not yet been submitted in full. Please include a copy of this letter with your NDA when it is submitted in its entirety. If FDA refuses to file the application or PhotoCure withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, PhotoCure should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether PhotoCure continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

April 12, 2001

VIA FEDEX

Ms. Kalyani Bhatt
Project Manager
Center for Drug Evaluation and Research
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

**RE: Request for Waiver of Pediatric Studies
IND 59,756 Serial #021**

Dear Ms. Bhatt:

PhotoCure ASA requests a full waiver of the requirements to conduct clinical studies to assess the safety and effectiveness of the drug Product Metvix™ Cream in pediatric populations for the treatment of Actinic Keratosis (AK). Of interest, Basal Cell Carcinoma (BCC) is listed as exempt from study in pediatric populations. Basal Cell Carcinoma like AK occurs in the elderly and is a result of sun exposure. PhotoCure understands that AK does not usually progress to BCC but both conditions require extensive and prolonged sun exposure. This request is made in accordance with §21 CFR 314.55 (c) (2) and based on the following:

1. BACKGROUND

Metvix™ Cream is effective in photodynamic therapy of AK in adults. Actinic keratoses are pre-malignant skin lesions, which may transform to malignant squamous cell carcinomas in 0.1 to 20% of patients who initially present within AK (Ref Frost, CA et al, infra vide). Actinic keratosis lesions are usually small, thin, erythematous, and desquamating and occur on atrophic skin. Lesions occur in multiple areas on the body but typically on previously sun exposed skin such as the face, scalp and hands. The typical patient is elderly with an open-air occupation, like fisherman or farmer. Actinic keratoses are almost never seen in the pediatric population. These lesions are rarely seen in patients younger than 30 years of age¹. Years of repeated sun exposure are required to provoke the pre-neoplastic state. Susceptible children or those who are fair skinned usually and are closely followed by their pediatrician and treated with sunscreens as the first line therapy, but this subset of children notwithstanding, years of sun exposure are required to damage the skin sufficiently to induce AK.

Of the five studies conducted outside Australia, which focused on the epidemiological aspects of solar or actinic keratosis, only one included data on patients younger than 20 years of age, and these data support a low prevalence of AK in children 16 years of age or less¹.

¹ Frost CA, Green AC, Epidemiology of Solar Keratosis. Br.J. Dermatology 1944;131:455-64

Because of the rare occurrence of AK in children, the high success rate, but less than optimal cosmetic outcome with surgical modalities, Metvix™ Cream is not likely to be used in substantial numbers of pediatric patients. Consequently, Metvix™ Cream qualifies for a full waiver of pediatric study requirements.

We therefore formally request that the FDA find that there is a reasonable basis on which to conclude that Metvix™ Cream meets the grounds for a full waiver of requirements for pediatric clinical studies in §21 CFR 315.55 (c)(2).

Consistent with the provisions for full waiver of requirements for pediatric assessments in §21 CFR 314.55 (c)(2), and with the Draft Guidance for Industry “Recommendations for Complying With the Pediatric Rule”, [§21 CFR 314.55 (a) and 601.279a] (Appendix A). PhotoCure offers the following information in support of our request for full waiver.

2. WAIVER

a. What Age Ranges Are Included In the Waiver Request?

PhotoCure requests a waiver of requirements to assess the effects of Metvix™ Cream for treatment of actinic keratosis in children 16 years of age and younger.

b. Reasons for Waiving the Pediatric Studies Requirements.

Actinic keratosis occurs only very rarely in the pediatric population. The estimated occurrence of the disease in children in the US is unknown but is considered rare (less than 1 in 10,000); a figure well below the cut-off point of 50,000 pediatric patients which the FDA has chosen as the definition of “a substantial number of pediatric patients” in the final rule, published December 2, 1998 (Federal Register/Vol. 63, No. 231 pp 66632) and is unlikely to be used in a substantial numbers of pediatric patients.

In addition, as PhotoCure discussed the waiver and its provisions with Division representative’s during the Pre-IND meeting held on August 2, 1999, and in our original IND submission on November 5, 1999. Briefly it would be impossible to study enough pediatric patients to produce statistically or clinically meaningful data. For these reasons we informed the Division during the Pre-IND meeting that we did not intend to enroll pediatric subjects in clinical trials conducted under the IND, and that we would be requesting a waiver of any requirements to study pediatric patients.

c. Justification for the Waiver.

Based on the information summarized above, PhotoCure certifies that Metvix™ Cream for the treatment of actinic keratosis in adults:

- Does not provide a large margin of therapeutic benefit over existing treatments for pediatric patients, and because of the low prevalence of AK in children is not likely to be used.
- Will not likely to be used in a substantial number of patients in the 16 years of age and under group.

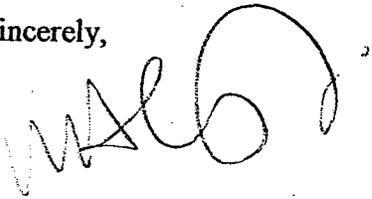
- In the absence of adequate labeling, could not pose significant risks to pediatric patients.

We also certify that the necessary studies are impossible or highly impractical because the number of patients in the 16 years and under age group is too small to provide statistically or clinically significant data.

The reasons are consistent with §21 CFR 314.55 (c)(2) and provides the FDA with a reasonable basis to conclude that several of the grounds for a waiver as specified in paragraph (c)(2) have been met and a waiver may be granted under those conditions.

If you have any questions or require any further information, please telephone me at (610)-581-7021.

Sincerely,



William A. Clementi, Pharm.D. F.C.P.
President
Clementi & Associates, Ltd

US Regulatory Agent PhotoCure ASA
cc: US and Norway Regulatory Files

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& Associates

VIA FACSIMILE AND FEDEX

RECEIVED

February 28, 2001

MAR 01 2002

MEGA/CDER

BB

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

NDA ORIG AMENDMENT

Re: Validation Report for PpIX Assay

Dear Ms Lutwak:

In response to the reviewer's request (Dr. Bashaw) for data on the validation of the PpIX assay and as we previously discussed on February 22nd, 2002, a report is attached. PhotoCure believes that this is the last of the outstanding requests made in the 2001 calendar year from the Division. The remaining outstanding CMC questions (which we received on February 19th, 2002) are being completed and will be forwarded to the Division as soon as possible.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

FDA Form 356h (No: 16)

CLEMENTI
& Associates

VIA FACSIMILE AND FEDEX

RECEIVED

FEB 27 2002

MEGA/CDER

February 20, 2001
2002

ORIG AMENDMENT

B2

Ms. Victoria Lutwak
Project Manager
Center for Drug Evaluation and Research (Room N242)
Division of Dental and Dermatological Drug Products
Food and Drug Administration (HFD 540)
9201 Corporate Blvd
Rockville, MD 20850

Re: ANSWERS TO FDA QUESTIONS FOR NDA 21-415 (Metvix[®] Cream)

Dear Ms Lutwak:

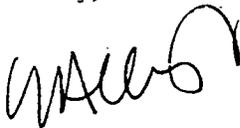
As requested, a compilation of previously submitted "responses" to the Division's questions sent during November and December 2001 are provided herein. Per our recent discussion, the only outstanding request is the validation report for PpIX assay methods. This is forthcoming and will be forwarded to the Division on or about February 28, 2002.

On February 6, 2002 prior FDA questions were re-sent to us and in response to that activity this compilation is provided. The response to each of the questions sent by the Division is appended in Tabs (A through G). The supporting information is ordered in accordance with the Divisions list of questions.

The Reviewer's Request for information regarding the number of patients enrolled in protocol PC T306/99 prior to the amendment of July 17, 2000 is also provided herein. Please note that the amendment was not a dosing amendment.

If you have any questions or require any additional information, please contact me at (610)-581-7021.

Sincerely,



William Clementi Pharm. D. F.C.P.
President
Clementi & Associates Ltd

US Regulatory Agent PhotoCure
cc: US and Norway Regulatory Files

FDA Form 356h (No: 11)

ORIGINAL

Answers to Questions *see next page*

The answers provided below have previously been provided to the Division as indicated, however each question and the data for that question are appended herein, except for Volume 21 of NDA 21-415.

1. Protocol and proposed label. FDA has PI but no container and carton e-file.

This information was submitted to the Division on October 25, 2001, containing the original draft package insert, tube and carton labels. They are found in NDA 21-415 Volume 1 pages 106, 107 and 119. They are found in Tab A herein. (A Diskette containing the carton e-file labels was forwarded to the Division on February 21, 2002.)

2. The application summary was provided as part of the NDA 21-415 submission

The Application Summary is provided in the NDA. The cover letter starting on page 4 and continuing to page 6 summarizes the contents of the submission. A copy of these pages are found in Tab B.

3. The Clinical Data Section

The clinical data section can be found in NDA 21-415 Volume 21 pages 1 to 271 (Not reproduced herein).

4. The Clinical Study Reports

The Clinical Data Summary and Results of Statistical Analysis are found in Volume 1 of NDA 21-415 on pages 205-258 and are found herein, Tab C.

5. The Sponsor should provide a site-breakdown of the data from the two pivotal multicenter studies. Did the Sponsor submit any of the above.

This data was provided in a submission dated December 19, 2001 titled Answers to Questions (Nov 26 & Nov 29, 2001) and are found herein, Tab D.

6. An electronic copy of the protocol.

A floppy disk was provided to the Division with the Protocols that were requested and has been received for by the Division (Sent via FEDEX on December 11, 2001 and delivery was confirmed).

7. A video training program used for investigators conducting the clinical trials?

The video tape was sent via FEDEX on December 17, 2001 and has been received by the Division (delivery was confirmed).

8. The Sponsor lists a Mutual Recognition Procedure, "Day 0" for European Countries. Please provide a brief explanation.

This question was answered in Item E in December 12, 2001 submission to the Division titled "Answers to Questions (Nov 26 & Nov 29, 2001) and are found herein, Tab D.

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9. **Provide detailed description about randomization/binding procedure for Study PC T305.**

This information (Item H in the FDA questions of November 26, 2001) was provided in the December 12, 2001 submission titled "Answers to Questions (Nov 26 and Nov 29, 2001)". This was sent via FEDEX on December 24, 2001 and was received by the Division on December 26, 2001 by T. Jennings, and are found herein, Tab E.

10. **Provide both ITT and PP analysis based on one-sided.**

This information (Item I in the FDA questions of November 26, 2001) as provide as part of the December 19, 2001 submission to the Division. This was part of the December 19, 2001 submission "Answers to Questions (Nov 26 and Nov 29, 2001) to the Division and are found herein, Tab E.

11. **Provide subgroup efficacy results by age and gender for each of the Studies PC T301, PC T302 and PC T305.**

This information (Item J in the FDA questions of November 26, 2001) was provided in the December 12, 2001 submission titled "Answers to Questions (Nov 26 and Nov 29, 2001)". This was sent via FEDEX on December 24, 2001 and was received by the Division on December 26, 2001 by T. Jennings. The data is contained herein, Tab E.

- new* 12. **Please provide a full report on the development and validation of fluorescence measurement methodology.**

An initial response (Item F in the FDA questions of November 26, 2001) was provided in the December 12, 2001 submission titled "Answers to Questions (Nov 26 and Nov 29, 2001)". This was sent via FEDEX on December 24, 2001 and was received by the Division on December 26, 2001 by T. Jennings and are found herein, Tab D. The validation report will be sent no later than February 28, 2002.

- new* 13. **In-vitro release study (Optional) but it may be helpful for the sponsor in future for SUPAC related issues.**

This information (Item G in the FDA questions of November 26, 2001) was provided in the December 12, 2001 submission titled "Answers to Questions (Nov 26 and Nov 29, 2001)". This was sent via FEDEX on December 24, 2001 and was received by the Division on December 26, 2001 by T. Jennings and are found herein, Tab D.

- new* 14. **Please provide a delineation of patients treated in PC T306/99 prior to the amendment of 7/17 (change of dosing).**

The listing of patients treated is provided in Tab F.

OFFICIAL SUBMISSION



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 2-11-01

To: William Clementi, Pharm.D.	From: Victoria Lutwak ✓
Company: Photocure ASA	Division of Dermatological and Dental Drug Products
Fax number: 610-581-7025	Fax number: 301-827-2075/ 827-2091
Phone number: 610-581-7021	Phone number: 301-827-2073
Subject: Request for information for NDA 21-415	

Total no. of pages including cover 4

Comments: Please see following page(s). If you have any question, please call me.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

2-19-02

Dear Dr. Clementi,

Please advise us when we can expect a response to the following request for information from the chemist-

Regards,

Vickey Lutwak

NDA 21-415
METVIX

Request for information:

The following are CMC Informational Requests (IRs) divided into either drug substance and drug product. To maintain the timeline required to meet PDUFA goals for this NDA, we ask for your responses by April 15, 2002. Please feel free to contact the Project Manager for NDA 21-415, Ms. Vickey Lutwak should you or the applicant have questions.

DRUG SUBSTANCE

1. Please provide the drug substance manufacturer's name, their full address, a contact name and telephone/fax numbers would be appreciated for administrative completeness.
2. The final drug substance, methyl aminolevulate HCl, the synthesis process (v.2, Item 4A.5.3, pp.48 & 51), however, there is no specification for specification was omitted? Explain why this specification was omitted?
3. The synthesis processes should be diagramed side-by-side to easily pick out the advantages and deficiencies of each process. A clear description of both the and should also be added.
4. Drug substance stability data had been generated on product stored in containers (v.3, p.131). However, shipment and intermediate storage occurs in containers. It is recommended the applicant consider conducting stability studies in the container
5. Please provide data to support manufacturing process (v.3, p.414).
6. Adjust your specification for the impurity
7. In v 4, p.171, describe in detail the Study located in the drug substance stability protocol section.
8. Were both the original drug substance and drug substance placed on stability and if so, what were their respective lot numbers and data?
9. Please describe in detail why the specification was changed from an

DRUG PRODUCT

1. Please contact the excipient vendors for each of the following drug product excipients: cholesterol, polyoxy - stearate, cetostearyl alcohol, glyceryl monostearate, isopropyl myristate and oleyl alcohol. If any of these excipients have bovine origins, please provide their country of origin, body part(s), and related International Sanitary Certificates.
2. In v.5,p.7, it was noted there was _____
/
3. In v.5, Tab 4B.4, p.51, additional data may be required. Please provide _____ of the peanut oil to be used in this drug product. Assurance is needed that the peanut oil excipient has either been refined _____ or the above analytical data should be submitted. The flow diagram in v.5, p.122 suggests _____
4. A sampling plan was submitted in v.6, Tab 4B.8, p.122, but lacked sufficient detail. Please provide a brief overall description of the sampling plan(s) for production batches and selection of sub-samples for analyses. Evaluation should consider the adequacy of the sampling process (e.g., beginning, middle, end) and the number of samples per production batch.
5. The _____ impurities _____ are reported to be _____ and therefore should be chemically identified.
/
6. Please provide a detailed _____
/
/
/

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-415.000
CMC Informational Requests

Page 4 of 3

10. We note that no drug product stability sampling was conducted at _____ at 2-8°C storage conditions in the _____ container as suggested in Table 4B.9.5-1, v.7, Tab 4B.9, page 13?

11. Primary Stability results _____ thus the need for 2-8°C storage conditions with a requested expiry date of _____

12. Under accelerated stability conditions (25°C/60%RH), _____

Provide the shipment and storage plans for this drug product.

13.

14.

15. The name, full address, telephone and fax numbers are needed for the individual responsible for providing the drug substance and drug product samples for methods validation studies.