

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-415**

**CHEMISTRY REVIEW(S)**

**NDA 21-415**

**Tradename (methyl aminolevulinate) Cream,  
168 mg/g**

**Photocure ASA**

**J. S. Hathaway, Ph.D.  
Division of Dermatological and Dental Drug Products  
HFD-540**



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## Chemistry Review Data Sheet

1. NDA 21-415
2. REVIEW #: 4
3. REVIEW DATE: 06-JAN-2004
4. REVIEWER: J. S. Hathaway, Ph.D.

### 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-SEP-2001
Telecon Request for Readiness Statement	16-OCT-2001
Telecon for EES CFN Numbers	30-OCT-2001
Telecon for Method Validation Documents	06-NOV-2001
Letter fulfilling Request for Revising Outline	14-NOV-2001
Amendment BC	02-APR-2002
Amendment NC	07-APR-2002
Amendment NC	23-MAY-2002
Review #1	28-JUN-2002
Review #2	23-JUL-2002
Review #3	26-JUL-2002
Microbiologist's Review	23-JUL-2002

### 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment AZ	17-JUL-2003
Amendment BC	17-JUL-2003
Amendment BC	21-NOV-2003



## CHEMISTRY REVIEW



### Chemistry Assessment Section

#### 7. NAME & ADDRESS OF APPLICANT:

Name: Photocure ASA  
Hoffsveien 48  
Address: N-0377, Oslo  
Norway  
Representative: William A. Clementi, Pharm.D.  
Clementi & Associates  
919 Conestoga Road  
Rosemont, PA 19010  
Telephone: 610-581-7021  
Fax:: 610-581-7025

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None  
b) Non-Proprietary Name (USAN): methyl aminolevulinate hydrochloride  
c) Code Name/# (ONDC only): P-1202  
d) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: 2  
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Non-hyperkeratotic actinic keratoses

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 168 mg/g or 16.8%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  X  Rx   OTC



# CHEMISTRY REVIEW



## Chemistry Assessment Section

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_\_ SPOTS product – Form Completed

X Not a SPOTS product

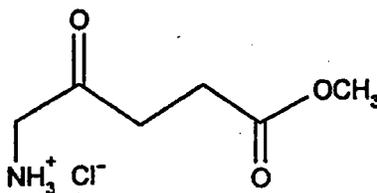
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methyl aminolevulinate hydrochloride

Molecular Weight: 181.62

Molecular Formula:  $C_6H_{11}NO_3 \cdot HCl$

Molecular Structure:



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	III			2	Not Applicable	Not Applicable	This DMF was erroneously labeled as a Type 3 and should be a Type 1.
—	III			3	Adequate	9/18/01	This DMF requires an updated list of authorized companies.

<sup>1</sup> Action codes for DMF Table:  
1 – DMF Reviewed.



# CHEMISTRY REVIEW



## Chemistry Assessment Section

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There was sufficient data within the application, therefore the DMF did not need review)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND for Dermatologic Diseases	59,756	IND for Metvix Cream

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Approval	07-JAN-2004	S. Adams
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	30-APR-2002	J. Vidra
OPDRA	NA		
EA	Categorical Exclusion Granted	10-MAY-2002	J. Vidra
Microbiology	AP	23-JUL-2002	B. Riley



# The Chemistry Review for NDA 21-415

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA may be Approved for the chemistry, manufacturing and controls (CMC) as submitted in the application and supporting documents. No outstanding CMC regulatory issues exist at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance:

The US Adopted Name (USAN) for the drug substance in Tradename (methyl aminolevulinate) Cream is methyl aminolevulinate hydrochloride, identified by the code P-1202 throughout the NDA. Methyl aminolevulinate hydrochloride is very soluble in water ( ) and has a sharp melting point (119.1°C) by

Impurities were identified and are controlled to amounts less than by weight.

##### (2) Drug Product:

Tradename (methyl aminolevulinate) Cream contains 168 mg methyl aminolevulinate, equivalent to 210 mg methyl aminolevulinate hydrochloride, per gram of cream. Tradename (methyl aminolevulinate) Cream is a

## Chemistry Assessment Section

cream containing a [redacted] emollient ingredients, [redacted] and methylparaben and propylparaben as preservatives. The excipients in Tradename (methyl aminolevulinate) Cream conform to compendial standards of the USP, NF, BP or Ph.Eur. monographs, and were not derived from animal sources, with the exception of [redacted]. The [redacted] and does not contain bovine material. The only non-compendial excipients in the drug product formulation were [redacted] Glyceryl Monostearate and Refined Almond Oil, both of which conformed to the BP and Ph.Eur. monographs for these materials, respectively. The peanut oil excipient was refined [redacted] and thus is not expected to contain detectable levels of allergenic proteins, [redacted].

The manufacturing process is straightforward. [redacted]

Several independent analytical methods are used to assay the drug substance and impurities arising from degradation. An HPLC assay method was developed for the drug substance and most of its [redacted] impurities. [redacted] methods were developed for [redacted] impurities.

The drug product is packaged in two different collapsible blind-end aluminum tubes [redacted] white screw-top cap with puncturing spike and [redacted]. The tubes differ primarily by their [redacted]. Both tubes containing Tradename (methyl aminolevulinate) Cream were placed on stability and found to be stable. [redacted]

An 18 month expiry date can be recommended for Tradename (methyl aminolevulinate) Cream as packaged in the [redacted] tubes when stored at 2-8°C and ambient humidity. A 15 month expiry date can be recommended for Tradename (methyl aminolevulinate) Cream as packaged in the [redacted] tubes when stored at 2-8°C and ambient humidity.

## Chemistry Assessment Section

The applicant claimed categorical exclusion under 21 CFR 25.31(b), which was subsequently granted, since the Expected Introduction Concentration was less than 1.0 ppb.

**B. Description of How the Drug Product is Intended to be Used**

Tradename (methyl aminolevulinate) Cream is claimed to be effective in the photodynamic therapy of actinic keratoses in adults. This drug product is a combination of Tradename (methyl aminolevulinate) Cream and a light activation device. During this review, this drug/device had CDER as the review lead. The device was reviewed under consult to CDRH.

The mechanism of action for methyl aminolevulinate in Tradename (methyl aminolevulinate) Cream involves its metabolic conversion to protoporphyrin IX (PPIX), which absorbs light in the visible range and is an active photosensitizer. Tradename (methyl aminolevulinate) Cream is applied on a 5 to 55 mm diameter spot, which is then illuminated by a broad spectrum light source in the 570-650 nm wavelength. A calibration probe is initially placed into the proposed treatment field to allow for proper exposure time. After application of Tradename (methyl aminolevulinate) Cream and exposure to the companion lamp device, the PPIX formed in the skin produces cytotoxic singlet oxygen-adduct species (photoactive porphyrins, or PAP) which destroy the target cells (for this indication, basal cell carcinomas).

The drug product was applied at concentrations of 16, 80 and 168 mg methyl aminolevulinate/gram Tradename (methyl aminolevulinate) Cream, with the latter concentration being selected for this drug product. Photoactivation generally occurs at 28 hours and within one hour of illumination the PAP concentration falls rapidly to or below baseline. This process, known as photobleaching, was complete after photoactivation at 48 hours.

At this time, the recommended expiration date for Tradename (methyl aminolevulinate) Cream is 18 months for product in \_\_\_\_\_ packages, and 15 months in \_\_\_\_\_ packages. Storage conditions for this cream in both the \_\_\_\_\_ collapsible aluminum tube is at 2-8°C and ambient humidity.

The question of Tradename (methyl aminolevulinate) Cream sterility arose during the review of NDA 21-415 when it became known that, in the course of preparation of the treatment site prior to application of the drug product, the skin surface was abraded to enhance absorption. A subsequent team meeting and consultation with the microbiology reviewer reached the conclusion that this drug product was not required to be sterile.



## CHEMISTRY REVIEW



### Chemistry Assessment Section

#### **C. Basis for Approvability or Not-Approval Recommendation**

Not applicable.

### **III. Administrative**

#### **A. Reviewer's Signature**

*(see attached electronic signature page)*

#### **B. Endorsement Block**

Chemist/JS Hathaway/Date: 06-JAN-2004  
ChemistryTeamLeader/WHDeCamp/  
ProjectManager/MHarris/

#### **C. CC Block**

cc: Original NDA 21-415  
HFD-540/DivDir/JKWilkin  
HFD-540/DermTeamLdr/MLuke  
HFD-540/MedOffr/BVaughan  
HFD-540/PharmTox/PBrown  
HFD-540/ProjMgr/MHarris  
HFD-540.Chem/JS Hathaway  
HFD-540/ChemTeamLdr/WHDeCamp

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Steve Hathaway  
1/9/04 09:55:48 AM  
CHEMIST  
AP rcommended  
For your concurrence

Wilson H. DeCamp  
1/9/04 10:09:28 AM  
CHEMIST  
concur with review; recommended action is AP if applicant  
accepts all labeling changes, AE otherwise

**NDA 21-415**

**Metvix (methyl aminolevulinate hydrochloride) Cream,  
168 mg/g**

**Photocure ASA**

**James D. Vidra, Ph.D.  
Division of Dermatological and Dental Drug Products  
HFD-540**



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<b>B. Endorsement Block.....</b>	<b>9</b>
<b>C. CC Block .....</b>	<b>9</b>
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# Chemistry Review Data Sheet

1. NDA 21-415
2. REVIEW #:3
3. REVIEW DATE: 26-Jul-2002
4. REVIEWER: James D. Vidra, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-Sep-2001
Telecon Request for Readiness Statement	16-Oct-2001
Telecon for EES CFN Numbers	30-Oct-2001
Telecon for Method Validation Documents	06-Nov-2001
Amendment BC	14-Nov-2001
Amendment BC	02-Apr-2002
Amendment BC	07-Apr-2002
Amendment BC	23-May-2002
Amendment BC	28-May-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
EER	25-Jul-2002



## CHEMISTRY REVIEW



### Chemistry Assessment Section

#### 7. NAME & ADDRESS OF APPLICANT:

Name: PhotoCure ASA  
Hoffsveien 48  
Address: N-0377, Oslo  
Norway  
William A. Clementi, Pharm.D.  
Representative: Clementi & Associates  
919 Conestoga Road  
Rosemont, PA 19010  
Telephone: 610-581-7021  
Fax: 610-581-7025

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Metvix Cream  
b) Non-Proprietary Name (USAN): Methyl aminolevulinate hydrochloride  
c) Code Name/# (ONDC only): P-1202  
c) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: 2  
• Submission Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Non-hyperkeratotic actinic keratoses

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 168 mg/g

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

# CHEMISTRY REVIEW

## Chemistry Assessment Section

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_\_\_ SPOTS product – Form Completed

X  Not a SPOTS product

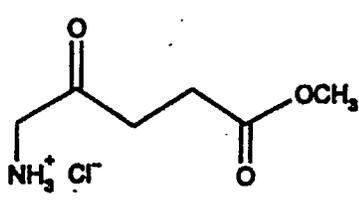
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methyl aminolevulinate hydrochloride

Molecular Weight: 181.62

Molecular Formula:  $C_6H_{11}NO_3 \cdot HCl$

Molecular Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	2	Not Applicable	Not Applicable	This DMF was erroneously labeled as Type 3 but should be a Type 1.
/	III			3	Adequate	9/18/01	This DMF requires an updated list of authorized companies.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF



# CHEMISTRY REVIEW



## Chemistry Assessment Section

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Dermatologic Diseases IND	59,756	IND for Metvix Cream

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	25-Jul-2002	Garcia
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	30-Apr-2002	Vidra
OPDRA	NA		
EA	Categorical Exclusion Granted	10-May-2002	Vidra
Microbiology	Consult requested & completed. Sterility not required for drug product.	17-Jun-2002	Cooney



# The Chemistry Review for NDA 21-415

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

An APPROVAL action is recommended for NDA 21-415.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance:

The USAN name for the drug substance in Metvix Cream is methyl aminolevulinate hydrochloride coded P-1202 throughout this NDA. Methyl aminolevulinate is soluble in water and has a sharp melting point (119.1oC) by

impurities are identified and controlled at less than

##### (2) Drug Product:

Metvix Cream contains 168 mg methyl aminolevulinate which corresponds to 210 mg methyl aminolevulinate hydrochloride/g cream. Metvix is a cream containing a emollients and methylparaben and propylparaben preservatives. The excipients in Metvix Cream conform to compendial standards of the USP, NF, BP or Ph.Eur. and were not derived from animal sources with the exception of The and did not contain bovine material. The only non-compendial excipients were the Glyceryl Monostearate and Refined Almond Oil, but both were BP and Ph.Eur respectively. The peanut oil excipient was refined and thus does not contain detectable levels of allergenic proteins.



## Chemistry Assessment Section

The manufacturing process is a straight-forward

Multiple analytical methods are used to assay the drug substance and degradant impurities. An HPLC assay method was developed for the drug substance and most of its impurities. methods were developed for the impurities.

The drug product is packaged in two different collapsible blind-end aluminum tubes screw top white cap with a puncturing spike and The tubes differ primarily by their Both tubes containing Metvix Cream were placed on stability and found to be comparable and stable.

Although a shelf life of was proposed by the applicant, an 18 month expiry date is recommended for Metvix Cream packaged in either the tubes when stored at 2-8°C/ambient humidity.

Establishment inspections have been completed for the facilities indicated in the application. An overall recommendation of Acceptable has been received from the Office of Compliance.

The applicant claimed categorical exclusion under 21 CFR 25.31(b) which was recommended for approval since the Expected Introduction Concentration was less than 1.0 ppb.

## B. Description of How the Drug Product is Intended to be Used

Metvix Cream is claimed to be effective in the photodynamic therapy of actinic keratoses in adults. Actinic keratoses are pre-malignant skin lesions which can be transformed into malignant squamous cell carcinomas in 0.1 – 20% of patients. This drug product is a combination of Metvix Cream and a light activation device. During this review, this drug/device has CDER as the review lead.

The mechanism of action for methyl aminolevulinate in Metvix Cream involves its conversion to protoporphyrin IX, an active photosensitizer. Upon light activation, the photosensitizer gives rise to the production of cytotoxic singlet oxygen species (photoactive porphyrins-PAP) which destroy the target cells of actinic keratoses. Metvix Cream is applied on a 5 to 55 mm diameter spot which is then illuminated by a broad spectrum light source in the 570-650 nm wavelength. A calibration probe is initially placed into the proposed treatment field to allow for proper exposure time.

**Chemistry Assessment Section**

The drug product was applied at concentrations of 16, 80 and 168 mg methyl aminolevulinate/gram Metvix Cream with the latter concentration being selected for this drug product. Photoactivation generally occurs at 28 hours and, within one hour of illumination, the PAP concentration falls rapidly to or below baseline. This process known as photobleaching was complete after photoactivation at 48 hours.

At this time, the recommended expiration date for Metvix Cream is 18 months. Storage conditions for this cream in either the \_\_\_\_\_ collapsible aluminum tube is at 2-8°C and ambient humidity.

The question of Metvix Cream sterility arose when it became known that the skin surface was abraded prior to application of the drug product. A team meeting with microbiology consult later determined the drug product did not require sterilization.

**C. Basis for Approvability or Not-Approval Recommendation**

The basis for the Approval recommendation is the acceptable manufacturing and controls for the drug substance and drug product, combined with the acceptable overall cGMP evaluation for the two foreign facilities.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

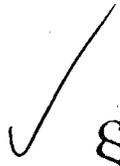
ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

**C. CC Block**

2   Page(s) Withheld



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

   § 552(b)(5) Deliberative Process

   § 552(b)(5) Draft Labeling

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

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Jim Vidra  
7/29/02 04:04:07 PM  
CHEMIST

10 Month PDUFA Date: 7/26/02. EER attachment added.

Wilson H. DeCamp  
7/29/02 04:18:03 PM  
CHEMIST  
concur with review; AP action recommended

**NDA 21-415**

**Metvix (methyl aminolevulinate hydrochloride) Cream,  
168 mg/g**

**Photocure ASA**

**James D. Vidra, Ph.D.  
Division of Dermatological and Dental Drug Products  
HFD-540**



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C. CC Block .....	9
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A. Informational Request #2 Responses.....	12
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# Chemistry Review Data Sheet

1. NDA 21-415
2. REVIEW #:2
3. REVIEW DATE: 23-Jul-2002
4. REVIEWER: James D. Vidra, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-Sep-2001
Telecon Request for Readiness Statement	16-Oct-2001
Telecon for EES CFN Numbers	30-Oct-2001
Telecon for Method Validation Documents	06-Nov-2001
Amendment BC	14-Nov-2001
Amendment BC	02-Apr-2002
Amendment BC	07-Apr-2002
Amendment BC	23-May-2002
Amendment BC	28-May-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment BC	23-May-2002



## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: PhotoCure ASA  
Hoffsveien 48  
Address: N-0377, Oslo  
Norway  
William A. Clementi, Pharm.D.  
Representative: Clementi & Associates  
919 Conestoga Road  
Rosemont, PA 19010  
Telephone: 610-581-7021  
Fax: 610-581-7025

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Metvix Cream  
b) Non-Proprietary Name (USAN): Methyl aminolevulinate hydrochloride  
c) Code Name/# (ONDC only): P-1202  
c) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: 2  
• Submission Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Non-hyperkeratotic actinic keratoses

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 168 mg/g

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_\_ SPOTS product – Form Completed

X  Not a SPOTS product

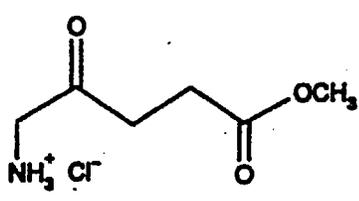
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methyl aminolevulinate hydrochloride

Molecular Weight: 181.62

Molecular Formula:  $C_6H_{11}NO_3 \cdot HCl$

Molecular Structure:



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	III	/	/	2	Not Applicable	Not Applicable	This DMF was erroneously labeled as Type 3 but should be a Type 1.
—	III	/	/	3	Adequate	9/18/01	This DMF requires an updated list of authorized companies.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Dermatologic Diseases IND	59,756	IND for Metvix Cream

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	31-Oct-2001	Garcia
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	30-Apr-2002	Vidra
OPDRA	NA		
EA	Categorical Exclusion Granted	10-May-2002	Vidra
Microbiology	Consult requested & completed. Sterility not required for drug product.	17-Jun-2002	Cooney

# The Chemistry Review for NDA 21-415

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 21-415 is Approvable from a chemistry viewpoint. The Approvable status may change when the formal inspection results have been received.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance:

The USAN name for the drug substance in Metvix Cream is methyl aminolevulinate hydrochloride coded P-1202 throughout this NDA. Methyl aminolevulinate is soluble in water; (t) and has a sharp melting point (119.1oC) by

impurities are identified and controlled at less than

##### (2) Drug Product:

Metvix Cream contains 168 mg methyl aminolevulinate which corresponds to 210 mg methyl aminolevulinate hydrochloride/g cream. Metvix is a cream containing a emollients, s and methylparaben and propylparaben preservatives. The excipients in Metvix Cream conform to compendial standards of the USP, NF, BP or Ph.Eur. and were not derived from animal sources with the exception of The and did not contain bovine material. The only non-compendial excipients were the Glyceryl Monostearate and Refined Almond Oil, but both were BP and Ph.Eur respectively. The peanut oil excipient was refined and thus does not contain detectable levels of allergenic proteins.

Executive Summary Section

The manufacturing process is a straight-forward

Multiple analytical methods are used to assay the drug substance and impurities. An HPLC assay method was developed for the drug substance and most of its impurities. , analytical methods were developed for the impurities.

The drug product is packaged in two different collapsible blind-end aluminum tubes and having an screw top white cap with a puncturing spike. The tubes differ primarily by their . Both tubes containing Metvix Cream were placed on stability and found to be comparable and stable.

Although a shelf life of as proposed by the applicant, an 18 month expiry date is recommended for Metvix Cream packaged in either the tubes when stored at 2-8°C/ambient humidity.

In the Establishment Inspection, the two facilities indicated in the application have not been inspected as of the date of this review. The inspection dates for the facility will be June 17-21, 2002 while June 24-28, 2002 is the inspection date for the drug product manufacturer, Penn Pharmaceuticals, Wales.

The applicant claimed categorical exclusion under 21 CFR 25.31(b) which was recommended for approval since the Expected Introduction Concentration was less than 1.0 ppb.

**B..Description of How the Drug Product is Intended to be Used**

Metvix Cream is claimed to be effective in the photodynamic therapy of actinic keratoses in adults. Actinic keratoses are pre-malignant skin lesions which can be transformed into malignant squamous cell carcinomas in 0.1 – 20% of patients. This drug product is a combination of Metvix Cream and a light activation device. During this review, this drug/device has CDER as the review lead.

The mechanism of action for methyl aminolevulinate in Metvix Cream involves its conversion to protoporphyrin IX, an active photosensitizer. Upon light activation, the photosensitizer gives rise to the production of cytotoxic singlet oxygen species (photoactive porphyrins-PAP) which destroy the target cells of actinic keratoses. Metvix



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§ 552(b)(5) Draft Labeling

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/s/

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Jim Vidra  
7/24/02 09:17:31 AM  
CHEMIST

Ten month PDUFA Date: 26-Jul-02. Review #2 format was  
modified.

Wilson H. DeCamp  
7/24/02 09:47:52 AM  
CHEMIST  
concur with review

**NDA 21-415**

**Metvix (methyl aminolevulinate hydrochloride) Cream,  
168 mg/g**

**Photocure ASA**

**James D. Vidra, Ph.D.  
Division of Dermatological and Dental Drug Products  
HFD-540**



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## CHEMISTRY REVIEW



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# Chemistry Review Data Sheet

1. NDA 21-415
2. REVIEW #: 1
3. REVIEW DATE: : 28-Jun-2002
4. REVIEWER: James D. Vidra, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	27-Sep-2001
Telecon Request for Readiness Statement	16-Oct-2001
Telecon for EES CFN Numbers	30-Oct-2001
Telecon for Method Validation Documents	06-Nov-2001
Amendment BC	14-Nov-2001
Amendment BC	02-Apr-2002
Amendment BC	07-Apr-2002
Amendment BC	23-May-2002
Amendment BC	28-May-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	27-Sep-2001
Amendment BC	14-Nov-2001
Amendment BC	02-Apr-2002
Amendment BC	07-Apr-2002
Amendment BC	23-May-2002
Amendment BC	28-May-2002



## Chemistry Assessment Section

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Photocure ASA  
Hoffsveien 48  
N-0377, Oslo  
Address: Norway

Representative: William A. Clementi, Pharm.D.  
Clementi & Associates  
919 Conestoga Road  
Rosemont, PA 19010  
Telephone: 610-581-7021  
Fax:: 610-581-7025

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Metvix  
b) Non-Proprietary Name (USAN): methyl aminolevulinate hydrochloride  
c) Code Name/# (ONDC only): P-1202  
d) Chem. Type/Submission Priority (ONDC only):  
• Chem. Type: 2  
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Non-hyperkeratotic actinic keratoses

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 168 mg/g

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  X  Rx   OTC



# CHEMISTRY REVIEW



## Chemistry Assessment Section

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

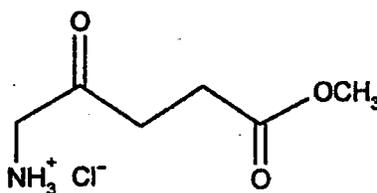
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methyl aminolevulinate hydrochloride

Molecular Weight: 181.62

Molecular Formula:  $C_6H_{11}NO_3 \cdot HCl$

Molecular Structure:



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	III	/		2	Not Applicable	Not Applicable	This DMF was erroneously labeled as a Type 3 and should be a Type 1.
—	III	/		3	Adequate	9/18/01	This DMF requires an updated list of authorized companies.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review



# CHEMISTRY REVIEW



## Chemistry Assessment Section

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There was sufficient data within the application, therefore the DMF did not need review)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND for Dermatologic Diseases	59,756	IND for Metvix Cream

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	31-Oct-2002	Garcia
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending	30-Apr-2002	Vidra
OPDRA	NA		
EA	Categorical Exclusion Granted	10-May-2002	Vidra
Microbiology	Consult requested and completed. Drug product sterility not required.	17-Jun-2002	Cooney



## The Chemistry Review for NDA 21-415

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

This NDA is Approvable from a chemistry viewpoint. The Approvable status of NDA 21-415 may change to Approval when:

- 1) Results from two international PAIs are available;
- 2) When the second list of Informational Requests has been reviewed.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

###### (1) Drug Substance:

The USAN name for the drug substance in Metvix Cream is methyl aminolevulinate hydrochloride coded P-1202 throughout this NDA. Methyl aminolevulinate is soluble in water ; — , and has a sharp melting point (119.1°C) . —

— impurities are identified and controlled at less than —



Chemistry Assessment Section

(2) Drug Product:

Metvix Cream contains 168 mg methyl aminolevulinate which corresponds to 210 mg methyl aminolevulinate hydrochloride/g cream. Metvix is a cream containing a emollients, and methylparaben and propylparaben preservatives. The excipients in Metvix Cream conform to compendial standards of the USP, NF, BP or Ph.Eur. and were not derived from animal sources with the exception of The and did not contain bovine material. The only non-compendial excipients were the Glyceryl Monostearate and Refined Almond Oil, but both were BP and Ph.Eur respectively. The peanut oil excipient was refined and thus does not contain detectable levels of allergenic proteins.

The manufacturing process is a straight-forward

Multiple analytical methods are used to assay the drug substance and degradant impurities. An HPLC assay method was developed for the drug substance and impurities. analytical methods were developed for the impurities.

The drug product is packaged in two different collapsible blind-end aluminum tubes and having an screw top white cap with a puncturing spike and. The tubes differ primarily by their. Both tubes containing Metvix Cream were placed on stability and found to be comparable and stable.

Although a shelf life of was proposed by the applicant, an 18 month expiry date is recommended for Metvix Cream packaged in either the tubes when stored at 2-8°C/ambient humidity.

In the Establishment Inspection, the two facilities indicated in the application have not been inspected as of the date of this review. The inspection dates for the facility will be June 17-21, 2002 while June 24-28, 2002 is the inspection date for the drug product manufacturer, Penn Pharmaceuticals, Wales.

The applicant claimed categorical exclusion under 21 CFR 25.31(b) which was recommended for approval since the Expected Introduction Concentration was less than 1.0 ppb.



Chemistry Assessment Section

**B..Description of How the Drug Product is Intended to be Used**

Metvix Cream is claimed to be effective in the photodynamic therapy of actinic keratoses in adults. Actinic keratoses are pre-malignant skin lesions which can be transformed into malignant squamous cell carcinomas in 0.1 – 20% of patients. This drug product is a combination of Metvix Cream and a light activation device. During this review, this drug/device has CDER as the review lead.

The mechanism of action for methyl aminolevulinate in Metvix Cream involves its conversion to protoporphyrin IX, an active photosensitizer. Upon light activation, the photosensitizer gives rise to the production of cytotoxic singlet oxygen species (photoactive porphyrins-PAP) which destroy the target cells of actinic keratoses. Metvix Cream is applied on a 5 to 55 mm diameter spot which is then illuminated by a broad spectrum light source in the 570-650 nm wavelength. A calibration probe is initially placed into the proposed treatment field to allow for proper exposure time.

The drug product was applied at concentrations of 16, 80 and 168 mg methyl aminolevulinate/gram Metvix Cream with the latter concentration being selected for this drug product. Photoactivation generally occurs at 28 hours and within one hour of illumination the PAP concentration falls rapidly to or below baseline. This process known as photobleaching was complete after photoactivation at 48 hours.

At this time, the recommended expiration date for Metvix Cream is 18 months. Storage conditions for this cream in either the \_\_\_\_\_ collapsible aluminum tube is at 2-8°C and ambient humidity.

The question of Metvix Cream sterility arose when it become known that the skin surface was abraded prior to application of the drug product. A team meeting is forthcoming to discuss whether this drug product should be sterile \_\_\_\_\_ or remain as is.

**C. Basis for Approvability or Not-Approval Recommendation**

The basis for the approvability rating is two-fold,e.g., 1) the lack of two \_\_\_\_\_ inspection results, and 2) the lack of applicant comments from a second CMC Informational Request.

**III. Administrative**

**A. Reviewer's Signature**



Chemistry Assessment Section

**B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

**C. CC Block**

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Jim Vidra  
6/28/02 07:26:44 PM  
CHEMIST

PDUFA Date: 26-Jul-2002 (10 months)

Wilson H. DeCamp  
7/1/02 08:25:57 AM  
CHEMIST

concur with review; note that an AP action must  
wait for completion of the inspections