CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022555Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-555

Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution
100 mg

PhotoCure ASA
Hoffsvein 48
NO-0377 Oslo
Norway

Ravindra K. Kasliwal, Ph.D.
Division of Pre-marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Division of Medical Imaging and Hematology

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Chemistry Review Data Sheet

1. NDA 22-555

2. REVIEW #: 2

3. REVIEW DATE: 11-May-2010

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Jun-2009
Resubmission	31-Mar-2010
Amendment	09-Apr-2010

7. NAME & ADDRESS OF APPLICANT

Name:	Photocure ASA
Address:	Hoffsvein 48 NO-0377 Oslo Norway Phone: +47 22 06 22 10
Representative:	Lynda Sutton CATO Research 4264 South Alston Avenue Durham, NC 27713
Telephone:	(919) 361-2286 – Phone (919) 361-2290 -Fax

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cysview
b) Non-Proprietary Name (USAN): Hexaminolevulinate hydrochloride
c) Code Name/# (ONDQA only): (b) (4) P-1206 (b) (4)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Photodiagnostic

11. DOSAGE FORM: for Intravesical Solution

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 100 mg (as HCl salt)

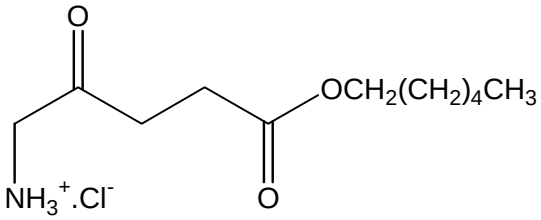
13. ROUTE OF ADMINISTRATION: Intravesicular into the bladder

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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: Hexyl aminolevulinate hydrochloride
Molecular Formula: $C_{11}H_{21}NO_3.HCl$
Relative Molecular Mass: 251.76

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TY-PE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	07-Feb-2006 (Dr. Ravindra Kasliwal)	None
	III			3	Adequate	08-Mar-1995 (Dr. Paul Dietz)	None
	V			7	N/A	N/A	Non product specific sterilization validation information – See micro review.
				3	Adequate	16-Mar-2006 (Dr. Ravindra Kasliwal)	None
	III			3	Adequate	20-Feb-2004 (Dr. Ravindra Kasliwal)	(b) (4) has been used previously with aqueous injectable drug product.
	III			4	N/A	N/A	N/A

(b) (4)	III	(b) (4)	4	N/A	N/A	N/A
	III		3	Adequate	16-Mar-2006 (Dr. Ravindra Kasliwal)	None

[1] 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
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
IND	51,224	This is applicant's IND for the drug product.
PMA	P050027	This drug product is to be used with a specific endoscope (D-light Photodynamic Diagnostic (PDD) System. The PMA is being reviewed concurrently with this NDA. This would be a combination product.
		(b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		
Pharm/Tox	N/A	N/A	Yanli Ouyang, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	Dosage form should be "For Intravesical Solution" and strength should be as HCl salt, i.e., 100mg/vial	18-Feb-2006	Guirag Poochikian, Ph.D. (b) (4)
Methods Validation	Package is included, however, methods do not need FDA lab validation.	N/A	N/A
OSE	Trademark Cysview is acceptable.	May 3, 2010	Anne Crandall, Pharm.D.
EA	Categorical exclusion is justified under 21 CFR 25.31 (b) and is acceptable	30-Nov-2009 (Chemistry Review # 1)	Ravindra K. Kasliwal, Ph.D
Microbiology	Approval	19-Oct-2009	Bryan S. Riely, Ph.D.

The Chemistry Review for NDA 22-555

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application was previously (see chemistry review #1) recommended for an approval action for manufacturing and controls under section 505 of the Act, provided an acceptable recommendation is obtained for manufacturing facilities from the CDER Office of Compliance. However, since previous recommendation the applicant changed the product reconstitution procedure (because of DMEPA product misadministration concerns), and has included a Luer-Lock catheter adapter (clinical division recommendation) as part of the kit. Subsequent to review of this change my recommendation remains the same. The application is recommended for an approval action for manufacturing and controls under section 505 of the Act, provided an acceptable recommendation is obtained for manufacturing facilities from the CDER Office of Compliance and labeling issues have been satisfactorily addressed.

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)

The drug product will be supplied as a **kit (in a box)** that would have one 10 mL glass vial of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution as a freeze-dried powder, one 50 mL polypropylene vial containing DILUENT for Cysview, and one Luer-Lock Catheter adapter. The Cysview powder vial contains 100 mg of lyophilized hexaminolevulinate hydrochloride corresponding to 85 mg hexaminolevulinate. The DILUENT is used to reconstitute the Cysview powder prior to administration. Upon reconstitution, the solution concentration of hexaminolevulinate hydrochloride is 2 mg/mL (8 mm solution). This solution strength was chosen as it provided the highest fluorescence intensity of the strengths studied.

The Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution vial only contains hexaminolevulinate hydrochloride as a lyophilized powder, and no other excipients. The DILUENT for Cysview is pH 6.0 (5.7-6.2) (b) (4) contains disodium phosphate, potassium dihydrogen phosphate, sodium chloride, hydrochloric acid and sodium hydroxide (b) (4) and water for injection. Both Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution vial and DILUENT for Cysview vial are supplied as sterile products. The acceptable shelf life of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution vial is 36 months (see chemistry review #1), DILUENT for Cysview in polypropylene (b) (4) vial is 36 months, when stored at controlled room temperature 20° -25°C. Hence the Kit should be labeled with a maximum of 36 month expiry. The reconstituted product solution has been shown to be stable for 2 hours when stored in a refrigerator (2°C -8°C) in the syringe.

(b) (4)

The drug substance is hexaminolevulinate hydrochloride (USAN Name) and has a molecular weight of 256.76. At various places in the NDA and in this review, this substance has been referred to as (b) (4) and compound P-1206.

Hexaminolevulinate hydrochloride itself is a white powder; however, the drug substance is characterized as a white to slightly yellow powder. (b) (4)

The pH of the solution of hexaminolevulinate hydrochloride needs to be controlled strictly and has been controlled (through specifications) very tightly between 5.7 and 6.2. (b) (4)

(b) (4) All batches used in pre-clinical and clinical studies were manufactured (b) (4). For commercial use, the drug substance will be manufactured (b) (4). The process has been successfully adapted to the new equipment at (b) (4). The synthetic route, the starting materials, the solvents, and the reagents are the same. There are no changes in the molar ratios of starting materials.

The drug substance is to be stored at 2 - 8°C (refrigerator) in inner packaging material of clear (b) (4) glass bottles with polypropylene screw caps. The bottles are stored inside (b) (4) aluminum barrier foil bags (b) (4) The retest period is (b) (4).

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

Cysview (hexaminolevulinate hydrochloride) for intravesical solution is a combination product that, in conjunction with blue light cystoscopy, is being developed as an additional diagnostic modality, to the already existent white light cystoscopic and biopsy procedures, for the detection of carcinoma in situ (CIS) of the bladder in patients with known or suspected superficial bladder cancer.

Prior to administration, Cysview powder must be reconstituted with the supplied DILUENT for Cysview at the site of use using aseptic conditions. The manner in which the finished product has been configured consists of Cysview powder in a 10 mL vial that is to be reconstituted with 50 mL of the solvent. The reconstitution procedure involves withdrawing all of the 50 mL solvent in a 60 mL syringe. Approximately 10 mL of this is then added to the vial of Cysview powder, and the powder is dissolved by gentle shaking. The entire reconstituted solution is then withdrawn back into the syringe. The appearance of the reconstituted solution is clear and colorless to pale yellow. The solution must be used immediately, or within 2 hours if stored at 2-8°C (36-46°F).

Prior to the instillation of Cysview, the bladder is drained. All 50 mL volume of reconstituted solution of Cysview is instilled into the bladder through a catheter inserted intravesically. The patient is then required to retain the fluid for a minimum of 60 minutes. Hexaminolevulinate is a precursor to heme biosynthesis. Several porphyrins occur as intermediates in this biosynthetic pathway. Since the formation of heme from the porphyrin-intermediates is regulated, porphyrins are expected to accumulate intracellularly in bladder wall lesions. The intracellular porphyrins are fluorescing compounds emitting red light upon excitation with blue light at wavelengths (b) (4) – 450nm. As a result, tumors (pre-malignant and malignant lesions) can be visualized as they will glow red on a blue background.

Executive Summary Section

Cysview is being developed for use with the Karl Storz Photodynamic Diagnosis (PDD) Device system with the D-Light light source. The device company has concurrently submitted a PMA for the Karl Storz Photodynamic Diagnosis (PDD) Device system. The cystoscopic device is equipped with the necessary filters to allow both standard white light cystoscopy and blue light (wavelength (b) (4) –450 nm) fluorescence cystoscopy.

C. Basis for Approvability or Not-Approval Recommendation

Cysview (hexaminolevulinate hydrochloride) for intravesical solution is recommended for an approval action from a CMC point of view, pending acceptable manufacturing facility inspection report. The approval action is based on:

- Adequate drug substance manufacturing and controls.
- Adequate drug product manufacturing and controls.
- Acceptable recommendation from Microbiology
- Acceptable container and carton draft labels.
- Acceptable insert labeling as it pertains to CMC.
- Acceptable justification for categorical exclusion under 21 CFR 25.31 (b) from performance of environmental assessment.

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Chemist's Name / Ravindra K. Kasliwal, Ph.D.
Chemistry LEAD / Eldon Leutzinger, Ph.D.
Chemistry Branch Chief Name / Ali Al Hakim, Ph.D.,
DMIDP Project Manager Name / James Moore

C. CC Block: Has been created in DFS.

4 Pages have been Withheld in Full as B4 (CCI/TS)
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

RAVINDRA K KASLIWAL
05/17/2010

ELDON E LEUTZINGER
05/17/2010

ALI H AL HAKIM
05/17/2010

NDA 22-555

Hexaminolevulinate Hydrochloride *Kit* for Intravesical Solution

PhotoCure ASA
Hoffsvein 48
NO-0377 Oslo
Norway

Ravindra K. Kasliwal, Ph.D.
Division of Pre-marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Division of Medical Imaging and Hematology

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-555

2. REVIEW #: 1

3. REVIEW DATE: 15-Dec-2009

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Jun-2009
Amendment	08-Sep-2009
Amendment	15-Sep-2009
Amendment	09-Dec-2009
Amendment	14-Dec-2009

7. NAME & ADDRESS OF APPLICANT

Name:	Photocure ASA
Address:	Hoffsvein 48 NO-0377 Oslo Norway Phone: +47 22 06 22 10
Representative:	Lynda Sutton CATO Research 4264 South Alston Avenue Durham, NC 27713
Telephone:	(919) 361-2286 – Phone (919) 361-2290 -Fax

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: HEXVIX® (not acceptable by DMEPA)
b) Non-Proprietary Name (USAN): Hexaminolevulinate hydrochloride
c) Code Name/# (ONDQA only): (b) (4) P-1206 (b) (4)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Photodiagnostic

Chemistry Review Data Sheet

11. DOSAGE FORM: for Intravesical Solution

12. STRENGTH/POTENCY: 100 mg (as HCL salt)

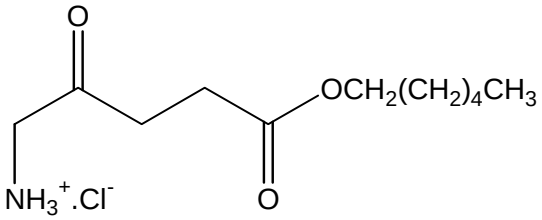
13. ROUTE OF ADMINISTRATION: Intravesicular into the bladder

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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: Hexyl aminolevulinate hydrochloride
Molecular Formula: $C_{11}H_{21}NO_3.HCl$
Relative Molecular Mass: 251.76

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TY-PE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		3	Adequate	07-Feb-2006 (Dr. Ravindra Kasliwal)	None
	III			3	Adequate	08-Mar-1995 (Dr. Paul Dietz)	None
	V			7	N/A	N/A	Non product specific sterilization validation information – See micro review.
				3	Adequate	16-Mar-2006 (Dr. Ravindra Kasliwal)	None
	III			3	Adequate	20-Feb-2004 (Dr. Ravindra Kasliwal)	(b) (4) has been used previously with aqueous injectable drug product.

(b) (4)	III	(b) (4)	4	N/A	N/A	N/A
	III		4	N/A	N/A	N/A
	III		3	Adequate	16-Mar-2006 (Dr. Ravindra Kasliwal)	None

[1] 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
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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
IND	51,224	This is applicant's IND for the drug product.
PMA	P050027	This drug product is to be used with a specific endoscope (D-light Photodynamic Diagnostic (PDD) System. The PMA is being reviewed concurrently with this NDA. This would be a combination product.
(b) (4)		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		
Pharm/Tox	N/A	N/A	Yanli Ouyang, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	Dosage form should be "For Intravesical Solution" and strength should be as HCl salt, i.e., 100mg/vial	18-Feb-2006	Guirag Poochikian, Ph.D. (b) (4)
Methods Validation	Package is included, however, methods do not need FDA lab validation.	N/A	N/A
OSE	Trademark Hexvix® is not acceptable.	02-Nov-2009	Anne Crandall, Pharm.D.
EA	Categorical exclusion is justified under 21 CFR 25.31 (b) and is acceptable	30-Nov-2009	Ravindra K. Kasliwal, Ph.D
Microbiology	Approval	19-Oct-2009	Bryan S. Riely, Ph.D.

Executive Summary Section

The Chemistry Review for NDA 22-555

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for manufacturing and controls under section 505 of the Act, provided an acceptable recommendation is obtained for manufacturing facilities from the CDER Office of Compliance.

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)

The drug product will be supplied as a **kit (in a box)** that would have one 10 mL glass vial of Hexaminolevulinate Hydrochloride powder as a freeze-dried drug substance and one 50 mL DILUENT for Hexaminolevulinate Hydrochloride vial (made either of glass or polypropylene). The Hexaminolevulinate Hydrochloride Powder vial contains 100 mg of lyophilized hexaminolevulinate hydrochloride as a powder corresponding to 85 mg hexaminolevulinate. The DILUENT is used to reconstitute the Hexvix Powder prior to administration. Upon reconstitution, the solution concentration of hexaminolevulinate hydrochloride is 2 mg/mL (8 mm solution). This solution strength was chosen as it provided the highest fluorescence intensity of the strengths studied.

The Hexaminolevulinate Hydrochloride Powder vial only contains hexaminolevulinate hydrochloride as a lyophilized powder, and no other excipients. The DILUENT for Hexaminolevulinate Hydrochloride is pH 6.0 (5.7-6.2) (b) (4) contains disodium phosphate, potassium dihydrogen phosphate, sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment), and water for injection. Both Hexaminolevulinate Hydrochloride Powder vial and DILUENT for Hexaminolevulinate Hydrochloride vial are supplied as sterile products. The acceptable shelf life of Hexaminolevulinate Hydrochloride powder vial is 36 months, DILUENT for Hexaminolevulinate Hydrochloride in glass vial is 36 months and for DILUENT for Hexaminolevulinate Hydrochloride in polypropylene (b) (4) vial is 36 months, both when stored at controlled room temperature 20° -25°C. Hence the Kit will need to be labeled with 36 month expiry. The reconstituted product solution has been shown to be stable for > 2 hours when stored in a refrigerator (2°C -8°C) in the syringe.

(b) (4)

The drug substance is hexaminolevulinate hydrochloride (USAN Name) and has a molecular weight of 256.76. At various places in the NDA and in this review, this substance has been referred to as (b) (4) and compound P-1206. Hexaminolevulinate hydrochloride itself is a white powder; however, the drug substance is characterized as a white to slightly yellow powder. (b) (4)

(b) (4)

The pH of the solution of hexaminolevulinate hydrochloride needs to be controlled strictly and has been controlled (through specifications) very tightly between 5.7 and 6.2. (b) (4)

(b) (4) All batches used in pre-clinical and clinical studies were manufactured (b) (4). For commercial use, the drug substance will be manufactured (b) (4). The process has been successfully adapted to the new equipment at (b) (4). The synthetic route, the starting materials, the solvents, and the reagents are the same. There are no changes in the molar ratios of starting materials.

The drug substance is to be stored at 2 - 8°C (refrigerator) in inner packaging material of clear (b) (4) glass bottles with polypropylene screw caps. The bottles are stored inside (b) (4) aluminum barrier foil bags (b) (4). The retest period is (b) (4).

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

Hexaminolevulinate Hydrochloride Kit for intravesical solution is a combination product that, in conjunction with blue light cystoscopy, is being developed as an additional diagnostic modality, to the already existent white light cystoscopic and biopsy procedures, for the detection of carcinoma in situ (CIS) of the bladder in patients with known or suspected superficial bladder cancer.

Prior to administration, Hexaminolevulinate Hydrochloride Powder must be reconstituted with the supplied DILUENT for Hexaminolevulinate Hydrochloride at the site of use using aseptic conditions. The manner in which the finished product has been configured consists of Hexaminolevulinate Hydrochloride Powder in a 10 mL vial that is to be reconstituted with 50 mL of the solvent. The reconstitution procedure involves withdrawing all of the 50 mL solvent in a 60 mL syringe. Approximately 5 mL of this is then added to the vial of Hexaminolevulinate Hydrochloride powder, and the powder is dissolved by gentle shaking. The reconstituted solution is then withdrawn into the syringe and after mixing in the syringe 5 mL of the solution is added again to the same vial to wash the vial and withdrawn back into the syringe. The procedure is repeated two times. The appearance of the reconstituted solution is clear and colorless to pale yellow. The solution must be used immediately, or within 2 hours when stored at 2-8°C (36-46°F).

Prior to the instillation of Hexaminolevulinate Hydrochloride solution the bladder is drained. All 50 mL volume of Hexaminolevulinate Hydrochloride solution is instilled into the bladder through a catheter inserted intravesically. The patient is then required to retain the fluid for a minimum of 60 minutes. Hexaminolevulinate is a precursor to heme biosynthesis. Several porphyrins occur as intermediates in this biosynthetic pathway. Since the formation of heme from the porphyrin-intermediates is regulated, porphyrins are expected to accumulate intracellularly in bladder wall lesions. The intracellular porphyrins are fluorescing compounds emitting red light upon excitation with blue light at wavelengths (b) (4) – 450nm. As a result, tumors (pre-malignant and malignant lesions) can be visualized as they will glow red on a blue background.

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Hexaminolevulinate Hydrochloride solutionis being developed for use with the Karl Storz Photodynamic Diagnosis (PDD) Device system with the D-Light light source. The device company has concurrently submitted a PMA for the Karl Storz Photodynamic Diagnosis (PDD) Device system. The cystoscopic device is equipped with the necessary

filters to allow both standard white light cystoscopy and blue light (wavelength (b) (4)–450 nm) fluorescence cystoscopy.

C. Basis for Approvability or Not-Approval Recommendation

Hexaminolevulinate Hydrochloride *Kit* for intravesical solution is recommended for an approval action from a CMC point of view, acceptable recommendation from Microbiology and pending acceptable manufacturing facility inspection report. The approval action is based on:

- Adequate drug substance manufacturing and controls.
- Adequate drug product manufacturing and controls.
- Acceptable container and carton draft labels.
- Acceptable insert labeling as it pertains to CMC (pending)
- Acceptable justification for categorical exclusion under 21 CFR 25.31 (b) from performance of environmental assessment.

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Chemist's Name / Ravindra K. Kasliwal, Ph.D.
Chemistry PAL / Eldon Leutzinger, Ph.D.
Chemistry Branch Chief Name / Sarah Pope Miksinski, Ph.D.
DMIRDP Project Manager Name / James Moore

C. CC Block : Has been created in DFS.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

RAVINDRA K KASLIWAL
12/15/2009

ELDON E LEUTZINGER
12/15/2009

Sarah Pope Miksinski
12/17/2009