

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022555Orig1s000

OTHER REVIEW(S)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: 1642-#1-A prospective, randomized, controlled clinical trial that will assess the safety and efficacy of repetitive use of Cysview in the detection of bladder cancer.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>May 2011</u>
	Study/Clinical trial Completion Date:	<u>July 2015</u>
	Final Report Submission Date:	<u>July 2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Expanded indication

Also safety of repetitive use both for the cysview and the blue light used in the cystoscope.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Repetitive use of cysview and the blue light not studied in the NDA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

N/A

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Safety of repetitive use
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

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

/s/

RENE C TYSON
05/28/2010

IRA P KREFTING
05/28/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: 1642-#2-A prospective, randomized, controlled clinical study that will assess the safety and efficacy of Cysview in the detection of carcinoma in situ of the bladder.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>May 2011</u>
	Study/Clinical trial Completion Date:	<u>July 2015</u>
	Final Report Submission Date:	<u>July 2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Expanded indication for detection with patients with in situ carcinoma

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Previous non-approved NDA studied patients with in situ carcinoma with equivocal efficacy results. Current NDA did not study the patient population of in situ carcinoma.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Population of patients with in situ carcinoma

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
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 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

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(signature line for BLAs)

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

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/s/

RENE C TYSON
05/28/2010

IRA P KREFTING
05/28/2010

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information	
NDA # 22555	
Established/Proper Name: Cysview Dosage Form: Intravesical Solution Strengths: 100 mg	
Applicant: Photocure ASA	
Date of Application: March 31, 2010 Date of Receipt: March 31, 2010	
PDUFA Goal Date: June 1, 2010	
Filing Date: May 28, 2010 Date of Filing Meeting: April 22, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3	
Proposed Indication: Cysview Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder. Referenced Hexvix - IND 51224, (b) (4), and CDRH - PMA P050027.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>Refer to Appendix A for further information.</i>	505(b)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	Class 1 - Resubmission
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product?	Drug/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 51224	
PDUFA and Action Goal dates correct in tracking	YES

<p>system?</p> <p><i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></p>	
<p>Are the proprietary, established/proper, and applicant names correct in tracking system?</p> <p><i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i></p>	YES
<p>Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?</p> <p><i>If not, ask the document room staff to make the appropriate entries.</i></p>	YES
Application Integrity Policy	
<p>Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</p> <p>If yes, explain:</p> <p>If yes, has OC/DMPQ been notified of the submission?</p> <p>Comments:</p>	<p>NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	YES
User Fee Status	Paid
<p><i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i></p>	
Exclusivity	
<p>Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<p>NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p>NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p>Not applicable (N/A)</p>
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p>NO</p> <p>NO</p> <p>NO</p>

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		NO	
If yes, please list below:			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		Electronic - eCTD	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		N/A	
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		YES	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		YES	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<p>YES</p> <p>YES</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p>YES</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<p>YES</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p>N/A</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments: PET 505(b)(2)</p>	<p>N/A</p>
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i></p>	<p>YES</p>

<p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will 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 application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (applies to paper submissions only)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p>N/A (electronic submission or no CMC technical section)</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<p>YES</p>
Pediatrics	
<p><u>PREA</u></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p>YES</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written</p>	<p>NO</p>

Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	Package Insert (PI) Vial labels
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	YES
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	YES <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	YES
MedGuide or PPI (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i> Comments:	N/A
REMS consulted to OSE/DRISK? Comments:	N/A
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	YES

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	N/A
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	N/A
<p>Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 22, 2010

NDA #: 22555

PROPRIETARY/ESTABLISHED NAMES: Cysview

APPLICANT: Photocure ASA

BACKGROUND: Cysview Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder. Referenced Hexvix - IND 51224, (b) (4), and CDRH - PMA P050027.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Thuy Nguyen, M.P.H.	Yes (Y)
	CPMS/TL:	Kaye Kang, Pharm.D.	No (N)
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Scheldon Kress, M.D.	Y
	TL:	Alex Gorovets, M.D.	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:	Anne Crandall, Pharm.D.	Y
	TL:	Melina Griffis, Pharm.D.	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Christy John, Ph.D.	Y
	TL:	Young-Moon Choi, Ph.D.	N
Biostatistics	Reviewer:	Tony Mucci, Ph.D.	Y
	TL:	Jyoti Zalkikar, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Adebayo Lanionu, Ph.D.	Y
	TL:	Adebayo Lanionu, Ph.D.	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ravi Kasliwal, Ph.D.	Y
	TL:	Eldon Leutzinger, Ph.D.	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	Robert Mello, Ph.D.	Y
	TL:	James McVey, Ph.D.	N
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other Reviewers	DDMAC – Michelle Sarafik, Pharm.D.		Y

OTHER ATTENDEES: Rafel Dwaine Rieves, M.D., DD, Shaw Chen, M.D., ONP, Mary Jo Cornelius, R.N., CDRH, Carol Holquist, R.Ph., OSE, Patricia Love, M.D., M.B.A., OCP

505(b)(2) filing issues? If yes, list issues:	N/A
Per reviewers, are all parts in English or English translation? If no, explain:	YES

<p>Electronic Submission comments</p> <p>List comments:</p>	<p>None</p>
<p>CLINICAL</p> <p>Comments: Labeling comments will be forwarded to Spon.</p>	<p>FILE</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p>If no, explain: 505(b)(2)</p>	<p>N/A</p>
<p>• Advisory Committee Meeting needed?</p> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>N/A (AC already in Rev Cycle 1)</p>
<p>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p>Comments:</p>	<p>Not Applicable</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p>N/A</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p>FILE</p>
<p>• Clinical pharmacology study site(s) inspections(s)</p>	

needed?	
BIostatistics Comments:	N/A
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	FILE
PRODUCT QUALITY (CMC) Comments: Labeling comments to Spon	FILE
<ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments: 	N/A
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments: 	YES YES
<ul style="list-style-type: none"> • Sterile product? If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	YES YES
FACILITY (BLAs only)	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: T.Nguyen (PM), Division Sign-off: R.Rieves (DD)	
GRMP Timeline Milestones: Filing Meeting - 04/22/10, Mid-Cycle – 05/06/10, Wrap-Up Meeting – 05/19/10	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Labeling comments will be forwarded to the Sponsor. *Class 1 Resubmission Due: June, 1, 2010
ACTIONS ITEMS	
X	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
X	Send labeling comments to Sponsor.
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

- (3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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/s/

THUY M NGUYEN
05/24/2010

MEMORANDUM

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

Date: 24-May-2010

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch VII, DNDQA-III

Through: Ali Al-Hakim, Ph.D.
Branch Chief
Branch VII, DNDQA-III

Sponsor: PhotoCure ASA.
Hoffsvein 48.
NO-0377 Oslo
Norway

Drug: Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg

Re: Facility inspection and resolution of labeling for NDA 22-555.

Remarks:

In the previous review (dated 11-May-2010), the application was recommended for an approval action for manufacturing and controls (CMC) 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. The Office of Compliance has now recommended that the manufacturing facilities associated with the manufacture and testing of this drug are acceptable (19-May-2010, see attached report). Additionally, the draft of the labels (text for Cysview powder vial, Cysview diluent vial, and Cysview Kit) submitted in the amendment dated 20-May-2010 has incorporated recommended changes and is acceptable for CMC. The package insert submitted in this same amendment also has incorporated CMC recommended changes and is acceptable. Hence the final recommendation for CMC is being amended as below.

Conclusions and Recommendations:

The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22555-000	Sponsor:	PHOTOCURE ASA
Org. Code:	100		4364 SOUTH ALSTON AVE
Priority:	3		DURHAM, NC 27713
Stamp Date:	30-JUN-2009	Brand Name:	HEXVIX
PDUFA Date:	01-JUN-2010	Estab. Name:	
Action Goal:		Generic Name:	HEXYL ANIMOLEVULATE
District Goal:	31-OCT-2009	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; HEXAMINOLEVULINATE; 85MG

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	R. KASLIWAL	Review Chemist	301-796-1386
	E. LEUTZINGER	Team Leader	301-796-1399

Overall Recommendation: ACCEPTABLE on 19-MAY-2010 by T. GOOEN (HFD-320) 301-796-3257

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:		
Profile:		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	06-OCT-2009	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:		
Profile:		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	31-AUG-2009	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:		
Profile:		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	18-DEC-2009	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:		
Profile:		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	14-SEP-2009	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:		
Profile:		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	07-DEC-2009	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: [REDACTED] (b) (4)

Profile: [REDACTED] OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-DEC-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: [REDACTED]

Profile: [REDACTED] OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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
05/24/2010

ALI H AL HAKIM
05/24/2010

FDA - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

REGULATORY HEALTH PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) LABELING REVIEW

Application Number: NDA 22555
Name of Drug: Hexaminolevulinate as Hydrochloride
Proprietary Drug Name: Pending
Applicant: Photocure ASA
Labeling Review Date: April 20, 2010

MATERIAL REVIEWED:

EDR Submission Date of Structure Product Labeling (SPL): March 31, 2010

Receipt Date: March 31, 2010

Type of Labeling Reviewed: WORD \ PLR

REVIEW SUMMARY

The Project Manager has completed a preliminary format review of the Sponsor's proposed labeling dated March 31, 2010, and concluded that the Sponsor is in compliance with the PLR format requirement.

RECOMMENDATIONS

FDA labeling comments \ edits will be forwarded to the Sponsor and a revised PLR labeling will be requested for further labeling discussions.

Review Completed By: Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager

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

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/s/

THUY M NGUYEN
05/18/2010

Memo to Record

Date: May, 18 2010
From: Xin Fu, Ph.D., D.A.B.T., CDRH/ODE/DRARD/ULDB
To: Michel Janda, Acting Branch Chief, CDRH/ODE/DRARD/ULDB
Subject: NDA22555 (P050027)
Company: Photocure, ASA

This consult is provided to Mr. Michel Janda in response to an intercenter request from Dr. Scheldon Kress, CDER, for consultative review of compatibility testing of a drug-device combination product, **Cysview** from Photocure, ASA, in conjunction with **Karl Storz D-Light C Photodynamic Diagnosis (PDD) System** from KSEA Endoscopy, America, Inc. (KSEA), in support of labeling review in NDA22555.

BACKGROUND

Cysview Solution, a drug-device combination product, is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

The labeling for Cysview is currently under review. To address compatibility of Cysview with instillation catheter, in the labeling, it states, "For bladder instillation of the solution of Cysview, use straight, or intermittent, urethral catheters with a proximal funnel opening that will accommodate the Luer Lock adaptor. Use only catheters made of vinyl (uncoated and coated with hydrogel), latex (amber and red), and silicone to instill the reconstituted Cysview. Do not use catheters coated or embedded with silver or antibiotics. In-dwelling bladder catheters (Foley catheters) may be used if the catheters are inserted shortly prior to Cysview administration and are removed following the Cysview instillation." To support such claim, the sponsor provide a report for compatibility testing of Hexvix® solution with catheters and Luer-Lock catheter adapters that may be used to administer.

The purpose of this review is to determine 1). whether the testing is sufficient to determine if there are any concerns for using the drug with catheter materials; 2). whether there are any limitations or cautions for the catheter that should be in the Cysview labeling. The review is conducted in reference to FDA Guidance for Industry "Container Closure Systems for Packaging Human Drugs and Biologics."

Cysview was previously reviewed under name of Hexvix in IND51224, (b) (4). Due to conflict with name of other product, it was recently re-named as Cysview. The Karl Storz PDD System is currently under review in P050027.

PRODUCT DESCRIPTION

The Cysview 85 mg Powder for Solution is to be used as a sterile solution for intravesical administration. The product is composed as a kit containing two vials:

- Cysview Powder, which is a sterile, freeze-dried, white to off white or pale yellow powder, is delivered as single dose, 10 mL vials with stoppers and aluminum seals. The powder is made by freeze-drying a sterile solution of the active substance in water for injections, contains 100

mg hexyl aminolevulinate hydrochloride (P-1206), corresponding to 85 mg of the active moiety hexyl aminolevulinate (HAL).

- 50 mL Solvent for Cysview for Intravesical Use, which is (b) (4) at pH 6.0 delivered in 50 mL vials. Solvent for Hexvix contains disodium phosphate, potassium dihydrogen phosphate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

The Cysview Powder is intended to be reconstituted with the Solvent for Cysview using a 50 mL syringe with a Luer-Lock tip and an appropriate gauge needle prior to administration. The recommended dosage for adults is 50 mL of reconstituted Cysview Solution instilled into the bladder via a urethral catheter. To ensure a stable catheter-syringe connection, the tapered end of a Luer-Lock adapter is inserted into the funnel end of the catheter. The Luer-Lock syringe with the reconstituted Hexvix Solution is connected to the catheter via the Luer-Lock end of the adapter. In practice instillation is completed within 1 minute.

COMPATIBILITY REVIEW

To determine the compatibility between the Cysview solution and the devices (urethral straight catheters and Luer-Lock adapters), the sponsor conducted tests according to the principles for compatibility testing provided in FDA Guidance for Industry "Container Closure Systems for Packaging Human drugs and Biologics".

In the testing, the Cysview solution was filled in the selected test devices, either a straight catheter or a Luer-Lock adapter made of different materials from different manufacturers, for 10 min, before the solution was emptied out of the device for further analysis as summarized in following table. Each test was run in triplicate.

Compatibility Assessment	Testing	Results
Loss of potency due to absorption or adsorption of the active drug substance to device surface	Compare P-1206 (the active ingredient of Cysview) concentration in the Cysview solution emptied from the test device with the concentration of a P-1206 reference sample using a validated chromatographic method.	No changes from reference sample in all test devices
Degradation of the active drug substance induced by leachables from device	Compare P-1206 and P-1201 (the degradation product of P-1206 (b) (4) (b) (4)) concentrations in the Cysview solution emptied from the test device with the concentrations of P-1206 and P-1201 reference samples using validated chromatographic methods.	No changes from reference sample in all test devices
Reduction in the concentration of an excipient due to absorption, adsorption, or leachable-induced degradation	Compare pH of Cysview solution emptied from test devices with reference sample (excipient are phosphate salts used to buffer the product pH)	No changes from reference sample in all test devices
Precipitation	Visual appearance of the Cysview solution emptied from test device	No changes in all test devices
Changes in drug product pH	Compare pH of the Cysview solution emptied from test device with pH in reference sample	No changes from reference sample in all test devices
Discoloration of dosage form or the device component	Visual appearance of the Cysview solution emptied from the test device	No changes in all test devices
Increase in brittleness of the device component	Visual examination of the test device after filled with the Cysview solution	No changes in all test devices

The test urethral catheters are listed below:



The test Luer-Lock adapters are listed below:



It concluded that the compatibility of urethral straight catheters with a funnel end composed of vinyl (uncoated and coated with hydrogel), latex (red and amber), and silicone, and of Luer-Lock catheter adapters composed of polypropylene and polyethylene, with Hexvix Solution (i.e., Cysview Solution) had been demonstrated.

Review Comment:

The compatibility testing was properly designed and conducted to evaluate the potential impact of the devices on the Cysview Solution. Representative devices in materials that are commonly used in urethral catheters and Luer-Locker adapters were tested. Although the evaluation on the impacts of the Cysview Solution on the devices was limited, because of the very short contact duration and the general inertness of the device materials, it is very unlikely that properties and performance of the catheters and adapters could be affected by the Cysview Solution. Further bench testing of the devices is not necessary. The results from the testing indicated that the Cysview Solution was compatible with the test urethral catheters and the Luer-Locker adapters.

REVIEW QUESTIONS

1. Whether the testing is sufficient to determine if there are any concerns for using the drug with catheter materials.

Comment – Although the testing cannot demonstrate that the Cysview Solution is compatible with all the urethral catheters and the Luer-Locker adapters, based on results from the testing along with the fact that no compatibility issue was raised during clinical studies, it is reasonable to believe that the concerns for using the Cysview Solution with catheter materials are minimal.

2. Whether there are any limitations or cautions for the catheter that should be in the Cysview labeling.

Comment – The statement of “Use only catheters made of vinyl (uncoated and coated with hydrogel), latex (amber and red), and silicone to instill the reconstituted Cysview” is not the most proper since vinyl, latex, and silicone are very general terms and they represent the materials that are typically used in the urethral catheters. It is suggested to be revised to “Compatibility testing demonstrated that the reconstituted Cysview Solution was compatible with the tested urethral catheters that were made of vinyl (uncoated and coated with hydrogel), latex (amber and red), and silicone from four different manufacturers.”



Xin Fu, Ph.D., D.A.B.T.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 4, 2010

To: Rafel Dwaine Rieves, MD, Acting Director
Division of Medical Imaging Products

Through: Melina Griffis, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Cysview (Hexaminolevulinate Hydrochloride) for Intravesical
Solution, 100 mg per vial

Application Type/Number: NDA 022555

Applicant/sponsor: Photocure ASA

OSE RCM #: 2010-841

CONTENTS

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1 METHODS AND MATERIALS REVIEWED	3
2 CONCLUSION AND RECOMMENDATIONS	3
2.1 Comments to the Applicant.....	3
APPENDICES	4

INTRODUCTION

The Division of Medication Error Prevention and Analysis evaluated the proposed container label, carton and insert labeling for Cysview (NDA 022555) which were revised based on the recommendations from OSE review # 2009-945. Our analysis of the labels and labeling identified vulnerabilities that could lead to medication errors. We provide recommendations in Section 2 with the aim of reducing the risk of medication errors with regards to the proposed product label and labeling.

1 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling submitted, March 31, 2010, as an amendment to the NDA submission. Our analysis of the labels also took into consideration our recommendations from the previous OSE review of the labels and labeling. This analysis compared our recommendations to the revised labels to ensure the changes were implemented correctly.

See Appendix A and B for images of proposed container labels and carton labeling.

2 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels and carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. We request the recommendations for the container labels and carton labeling in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Catherine Carr, at 301-796-2311.

2.1 COMMENTS TO THE APPLICANT

1. We have the following recommendations to prevent the Diluent from being mistaken as the active ingredient:
 - a. Remove the box from the principal display panel [REDACTED] (b) (4)
 - b. Relocate the [REDACTED] (b) (4) statement which is located in the upper area of the principal display panel so that it is more center. Furthermore, revise the statement so that it appears more prominent than “Cysview”.
 - c. Decrease the prominence of the proprietary name, “Cysview”, on the principal display panel.
 - d. Remove the established name and the route of administration from the principle display panel.
2. Carton Label

Revise the statement on the principle display panel which describes storage of the solution after reconstitution [REDACTED] (b) (4)

4 Pages Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

ANNE CRANDALL
05/04/2010

MELINA N GRIFFIS
05/04/2010

DENISE P TOYER
05/05/2010

CAROL A HOLQUIST
05/05/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: April 8, 2010

To: Thuy Nguyen, MPH – Senior Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: NDA 22-555
DDMAC labeling comments for Cysview (hexaminolevulinate as hydrochloride) Kit for the Preparation of Cysview Solution for Intravesical Use (8 mmol/L)

DDMAC has reviewed the revised proposed product labeling (PI) and revised proposed carton and container labeling for Cysview (hexaminolevulinate as hydrochloride) Kit for the Preparation of Cysview Solution for Intravesical Use (8 mmol/L) (Cysview) dated March 31, 2010, and submitted for consult via e-mail on April 7, 2010. We offer the following comments.

Highlights

(b) (4) Warnings and Precautions

1. What is the sponsor's rationale for qualifying Cysview's Warnings and Precautions **(b) (4)**? We recommend deleting **(b) (4)** for consistency with 21 CFR 201.57.

Full Prescribing Information

(b) (4) Warnings and Precautions

1. Please see comment above.

Adverse Reactions

Postmarketing Experience

1. **(b) (4)**

(b) (4) minimizes the risks of Hexvix therapy and is promotional in tone. Therefore, we recommend deleting.

Drug Interactions

1. (b) (4)

(b) (4)

Patient Counseling Information

1. (b) (4)

This claim minimizes the risks of Hexvix therapy and is promotional in tone. We recommend deleting this claim and either deleting this section or replacing the above text with a recommendation to educate patients about the drug's most common adverse reactions.

Carton and Container Labeling

DDMAC has reviewed the revised proposed carton and container labeling and has no comments at this time.

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

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/s/

MICHELLE L SAFARIK
04/08/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: December 14, 2009

TO: Thuy Nguyen, Regulatory Project Manager
Sheldon Kress, M.D., Medical Officer
Division of Medical Imaging and Hematology Products

FROM: Susan D. Thompson, M.D., Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-555

APPLICANT: Photocure ASA
Hoffsveien 48
N-0377 Oslo, Norway

DRUG: Hexvix Solution (hexaminolevulinate hydrochloride)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis system, as adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

CONSULTATION REQUEST DATE: August 18, 2009

DIVISION ACTION GOAL DATE: December 30, 2009

PDUFA DATE: December 30, 2009

I. BACKGROUND:

Hexvix solution is a diagnostic imaging agent for intravesical administration for use with photodynamic blue light cystoscopy as an adjunct to white light cystoscopy. Intravesical administration of Hexvix results in intracellular accumulation of porphyrins in lesions. These porphyrins are fluorescing compounds that emit red light upon excitation by blue light. In the human bladder, there is a greater accumulation of porphyrins in lesions when compared to normal urothelium. As a result, pre-malignant and malignant lesions glow red on a blue background.

The current standard of care for diagnosing bladder cancer is a combination of urine cytology, visual inspection of the bladder with an endoscope, and white light illumination (white light cystoscopy) and biopsies for histological verification. The sponsor proposes that Hexvix with photodynamic blue light cystoscopy, used as an adjunct to white light cystoscopy, will provide a better method of early tumor detection, allow for a more complete initial diagnosis, more effective tumor resection, and a more appropriate treatment plan for the patient, thus decreasing early recurrence rates and preventing the patient from undergoing further resections.

In clinical studies with Hexvix, the most frequent adverse events were bladder spasm (reported in 2.2% of patients) followed by dysuria, hematuria, bladder pain, procedure pain, urinary retention, and headache. Additional serious events reported included tachycardia, chest pain, pyrexia, hematuria, lung disorder, and sepsis. Cases of anaphylactoid shock, bladder pain, cystitis, and abnormal urinalysis have been reported in post marketing reports from other regions.

The sponsor proposes to use 50 mL of reconstituted Hexvix Solution instilled into the bladder via catheter with a 1 hour retention time, followed by white light and photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnostic (PDD) system as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder in patients with known or suspected bladder cancer.

The protocol inspected was: Protocol number PC B305/04 "A Randomized, Comparative, Controlled Phase III, Multicenter Study of Hexvix Fluorescence Cystoscopy and White Light Cystoscopy in the Detection of Papillary Bladder Cancer and the Early Recurrence Rate in Patients with Bladder Cancer." Please see the original Clinical Inspection Summary dated October 29, 2009 for further details of the Background and the Protocol.

II. RESULTS (by Site):

Since the submission of the original Clinical Inspection Summary (CIS), the Establishment Inspection Report (EIRs) have been received for Theodoris Maria de Reijke, Edward M. Messing, and the sponsor Photocure ASA. In addition, response letters to the Form FDA 483 were received from Dr. de Reijke and Photocure ASA. Please see the CIS completed on October 29, 2009 for a full summary of these inspections. Pertinent new information is given

below regarding the inspections of the sponsor, Photocure ASA, as well as a brief update on the inspection of Dr. de Reijke. No new information has been received regarding the inspection of Dr. Gomella; please see the CIS dated October 29, 2009 for a summary of this inspection. In addition, receipt of the EIR for Dr. Messing's inspection does not change the conclusions presented in the original CIS.

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Interim Classification	Final Classification
Theodoris Maria de Reijke Academic Medical Center Department of Urology Meibergdreef 9 1105 AZ Amsterdam The Netherlands	Study PC BC305/04 Site #403 12 subjects	10/12/09-10/16/09	VAI	Pending
Edward M. Messing, MD University of Rochester Medical Center Department of Urology 601 Elmwood Avenue, #656 Rochester, New York 14642	Study PC B305/04 Site #010 11 subjects	9/28/09-9/30/09	NAI	NAI
Leonard Gomella, MD Department of Urology Jefferson Medical College, Suite 1102 1025 Walnut Street Philadelphia, PA 19107	Study PC B305/04 Site #008 8 subjects	End 10/19/09	NAI	Pending
Photocure ASA Hoffsveien 48 N-0377 Oslo, Norway	Study PC B305/04	10/19/09-10/23/09	VAI	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

**1. Theodoris Maria de Reijke
Academic Medical Center
Department of Urology
Meibergdreef 9
1100 AD Amsterdam
Amsterdam 1100, Netherlands**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 30 subjects randomized and

enrolled; 29 subjects completed the study and 1 subject could not be catheterized. A 100% review of signed Informed Consent Documents and Case Report Form (CRF)/source documents was completed. The observations noted are based on discussions with the FDA field investigator, the Form FDA 483, the EIR, and Dr. de Reijke's written response dated October 27, 2009. There were no limitations to the inspection.

- b. **General observations/commentary:** There were three Serious Adverse Events (Angina pectoris, Urinary Retention with Blood Clot, and Hematuria at this site); all were properly documented and reported to the sponsor. No major discrepancies between data available at the site and listings provided with the assignment were noted. However, several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan in accordance with 21 CFR 312.60 and failed to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related tests. In his written response of October 27, 2009, Dr. de Reijke agreed with all of the observations on the Form FDA 483, with the exception of the item discussed below. The remaining items cited on the Form FDA 483 were discussed in the CIS dated October 29, 2009, and are not reiterated here.

Protocol Violations [21 CFR312.60]

1. The protocol prohibits concomitant use of Mitomycin. Subjects #015 and 017 were treated with Mitomycin, and these events were not documented as protocol violations by the CRO.

Medical Officer's Comment: In Dr. de Reijke's written response of October 27, 2009, Dr. de Reijke notes that administration of Mitomycin C was not prohibited after Visit 2a; his patients received the Mitomycin C between Visit 3 and Visit 4, which is not in violation of the protocol (Final protocol, page 33).

- c. **Assessment of data integrity:** Although protocol and Informed Consent Document violations occurred at this site, it is unlikely that these errors significantly impacted efficacy or safety outcomes of the study. This conclusion is unchanged after review of the EIR and Dr. de Reijke's written response.

**2. Photocure ASA
Hoffsveien 48
N-0377 Oslo, Norway**

- a. **What was inspected:** The FDA investigator reviewed Photocure ASA procedures and records for Protocol PC BC305/04. The inspection began on October 19, 2009 and was concluded on October 23, 2009. During the inspection, the inspector reviewed documentation on file pertaining to five of the participating sites, including the three clinical investigators inspected for this NDA. The data from two additional sites were reviewed: Site #016 Dr.

Mark Soloway and Site #304 Dr. Wolfgang Rosseler. The observations noted are based on discussions with the FDA field investigator, the Form FDA 483, the EIR, and Photocure ASA's written response dated November 5, 2009.

- b. **General observations/commentary:** The investigation documented that the sponsor failed to ensure proper monitoring of the study, and a Form FDA 483 was issued for this violation. Several other issues were presented in the EIR, but not listed on the Form FDA 483. In Photocure's written response dated November 5, 2009, monitoring of the site described in the Form FDA 483 is outlined.

Failure to ensure proper monitoring of an investigational study [21 CFR 312.56(a)]

The Form FDA 483 states "Per the Monitoring Plan, Version 1.0, updated April 25, 2005 the monitoring visit requirement was to conduct a visit during the active enrollment period after every 5 completed subjects not to exceed 6 completed subjects. No monitoring visit was conducted at Site #016 from June 06 until January 07. During the referenced period the site was actively engaged in the conduct of study related activities. Upon re-initiating the monitoring visits in January 07 it was disclosed the site had not been operating in compliance with the study protocol requirements." The sponsor's written response of November 5, 2009 acknowledges that a scheduled monitoring visit to Site #016 [REDACTED] (b) (4) was missed. They note that corrective actions taken after realizing that the visit was missed included increasing the frequency of monitoring visits to ensure that patients enrolled from June until December 2006 were monitored. When Photocure ASA was informed of protocol deviations at the site, discussions were initiated with the investigator (Dr. Mark Soloway) and an investigational site audit was performed in May 2007. The sponsor also notes that only 1 additional visit should have been performed during the gap in monitoring visits. In all, 18 visits were completed for this site during the study. See below for additional discussion of the specific protocol violations noted at this site.

Medical Officer's Comment: Although the gap in monitoring is clearly of concern, the sponsor took appropriate follow-up action to ensure that monitoring was resumed and intensified, as well as addressing protocol violations noted to occur during the gap in monitoring. Since failure to assure appropriate monitoring was not noted at other clinical sites inspected for NDA 22-555 and since Photocure ASA appropriately addressed the gap in monitoring, it does not appear that inadequate monitoring compromised data integrity at Dr. Soloway's site nor was it a systematic problem in this clinical trial.

Protocol violations documented on monitoring reports pertaining to the five sites reviewed included in the EIR but not on the Form FDA 483 include:

1. Failure to collect biopsies to confirm tumor recurrence – Dr. de Reijke Site #403 (see discussion above) and Dr. Soloway Site #016. At Dr. Soloway’s site, it was noted during monitoring on 2/21-2/23/2007 that the site sometimes failed to obtain biopsies of lesions observed during follow-up visits. Specifically, Dr. Soloway preferred to fulgurate rather than biopsy some lesions. This issue was discussed with him on several occasions, and the monitoring reports included with the Exhibits appear to reflect compliance, in that fewer lesions are reported as fulgurated, not biopsied. The monitoring records indicate that the following subjects at Dr. Soloway’s site had lesions fulgurated, but not biopsied:

016007 (b) (6), 016010 (b) (6), 016011 (b) (6), 016015 (b) (6), 016017 (b) (6), 016022 (b) (6), 016026 (b) (6), 016029 (b) (6), 016031 (b) (6), and 016048 (b) (6).

Medical Officer’s Comment: This information was communicated to the Review Team on December 3, 2009. The inspector was informed that subjects with missing biopsies were treated in the efficacy analysis according to a “worst case scenario” – i.e., in the efficacy analysis, they were treated as having tumors at follow-up cystoscopy in the ITT analysis and as nonevaluable in the per protocol analysis. This should be confirmed by the review division.

2. Administration of chemotherapy agents not in accordance with protocol requirements: For discussion of the findings at Dr. de Reijke’s site, see above. The inspector notes that several patients were appropriately excluded from the Per Protocol analysis at Dr. Gomella’s site for receipt of BCG treatment at Visit 4 or Mitomycin C at Day 0.

Medical Officer’s Comment: These protocol violations appear to have been handled appropriately by the sponsor.

3. Failure to videotape the transurethral resection of the bladder (TURB) procedures: Noted at the sites of Dr. de Reijke, Rosseler, and Soloway.

Medical Officer’s Comment: The outcome of this procedure does not produce data required for the primary efficacy outcome, as such, it is unlikely to impact study outcome.

4. Failure to perform the study follow-up visits within the protocol specified window: Noted at Dr. Messing’s site.

The Informed Consent forms at the sites of Dr. Gomella, Messing, and Soloway did not reflect the risk “for not using chemotherapeutic agents”, and at Dr. Messing’s site, did not include planned videotaping during transurethral resection, and Dr. Soloway’s site the updated Informed Consent Form describing the videotaping process was not used for ten subjects.

Medical Officer’s Comment: Review of the literature for treatment of bladder cancer does not indicate that it is mandatory to utilize intravesicular instillation of chemotherapeutic agents at the time of cystoscopy as an

adjunct to therapy. Therefore, it is not necessary to include this in an Informed Consent Document. The inspector did not include documentation that ten subjects at Dr. Holloway's site signed an outdated Informed Consent Document, although both blank versions of the forms were included. A study monitoring report dated February 21-23, 2007 included in the exhibits includes this observation, with a plan to advise each of the 10 patients and ask them to sign the revised Informed Consent Document.

K10

- c. **Assessment of data integrity:** The data collected and maintained at the Photocure ASA's site, as it pertains to the three clinical sites inspected in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348. 810 appear consistent with that submitted to the agency as part of and in support of NDA 22-555. It is unlikely that the deficiencies identified in the Form FDA 483 and in the EIR will impact data integrity. The review team should confirm that subjects 016007 (b) (6), 016010 (b) (6), 016011 (b) (6), 016015 (b) (6), 016017 (b) (6), 016022 (b) (6), 016026 (b) (6), 016029 (b) (6), 016031 (b) (6), and 016048 (b) (6) were treated as having tumors at follow-up cystoscopy in the Intent to Treat analysis and as nonevaluable in the Per Protocol analysis, as stated by the sponsor during the inspection.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the sites of Drs. de Reijke, Messing, and Gomella revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations regarding protocol violations and informed consent violations at Dr. de Reijke's site; additional protocol violations were identified at the site of Dr. Mark Soloway (Site # 016) during the inspection of the sponsor Photocure ASA. The most serious violation at both sites was the failure to biopsy all identified bladder lesions, thus potentially underestimating tumor recurrence rates. Of note, such failure to obtain histopathological documentation of tumors occurred in both study arms. The patient identification numbers of those not biopsied by Dr. de Reijke were provided to the review division Medical Officer on October 22, 2009 and in the CIS dated October 29, 2009. The current CIS addendum identifies those subjects not biopsied at Dr. Soloway's site. According to the sponsor's representative during the sponsor inspection, these subjects were treated as having a bladder tumor at follow-up in the Intent to Treat analysis and as nonevaluable in the Per Protocol analysis.

The remainder of the data from the subjects at the three inspected sites may be used in support of the indication.

Follow-Up Actions: The EIR for Dr. Gomella's site has not yet been received. If conclusions change after receipt and review of the EIR, a second CIS Addendum will be

generated.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

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/s/

SUSAN D THOMPSON
12/14/2009

TEJASHRI S PUROHIT-SHETH
12/15/2009

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: August 20, 2009

To: Trinh Scott - Regulatory Project Manager
Division of Medical Imaging and Hematology Products (DMIHP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 22-555
DDMAC labeling comments for Hexvix (hexaminolevulinate as hydrochloride) Kit for the Preparation of Hexvix Solution for Intravesical Use (8mmol/L)

DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Hexvix (hexaminolevulinate as hydrochloride) Kit for the Preparation of Hexvix Solution for Intravesical Use (8 mmol/L) (Hexvix) dated June 30, 2009, and submitted for consult on August 13, 2009. We offer the following comments.

Highlights

Indications and Usage

1. We recommend specifying that the drug's proposed usage is in "patients with known or suspected bladder cancer" for consistency with the proposed PI.

Adverse Reactions

1. We note that the sponsor separates bladder spasm, which occurred in <3% of patients, and other common adverse reactions, which occurred in ≤2% of patients. For clarity, and for consistency within this section of Highlights and with the proposed PI, we recommend revising "<3%" to ">2%" or "2.2%."

Use in Specific Populations

1. We recommend revising "[REDACTED] (b) (4) The [REDACTED]

proposed phrase is too definitive in nature and is inconsistent with the proposed PI.

2. According to the *Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements*, “Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, children) should not be included under this heading.” Therefore, we recommend deleting [REDACTED] (b) (4)

Full Prescribing Information

[REDACTED] (b) (4)

[REDACTED] (b) (4) we recommend deleting.

Drug Interactions

[REDACTED] (b) (4)

Overdosage

1.

(b) (4)

Does this statement belong in this section of the proposed PI? Is this information critical for the health care professional to be aware of? If not, we recommend deleting as it is promotional in tone.

2.

(b) (4)

Is this phrase accurate? If not, we recommend deleting. Please also see the Nonclinical Toxicology – Animal Toxicology and/or Pharmacology section of the proposed PI for a similar phrase.

Clinical Studies

(b) (4)

(b) (4)

We recommend presenting the results of the study without any qualifiers.

Patient Counseling Information

1.

(b) (4)

(b) (4)

. We recommend deleting this claim and replacing it with a

recommendation to educate patients about the drug's most common adverse reactions.

Carton and Container Labeling

DDMAC has reviewed the proposed carton and container labeling and has no comments at this time.

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/s/

MICHELLE L SAFARIK

08/26/2009

DARRTS copy of signed PDF sent via e-mail on August 20, 2009.

DSI CONSULT: Request for Clinical Inspections

Date: August 18, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Cynthia Kleppinger, M.D., Medical Officer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Scheldon Kress, M.D., Clinical Reviewer
Alexander Gorovets, M.D., PhD, Clinical Team Leader
Rafel Dwaine Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products, HFD-160
Office of Oncology Drug Products

From: Trinh Scott, Regulatory Project Manager, HFD-160

Subject: **Request for Clinical Site Inspections**
Hexvix (hexaminolevulinate)

I. General Information

Application#: **NDA 22-555**

Applicant: **Photocure ASA**

Contact: **Lynda Sutton (US Agent: Cato Research, Ltd.), (919) 361-2286, Lsutton@cato.com**

Drug Proprietary Name: Hexvix (New molecular Entity)

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

PDUFA: December 30, 2009

Action Goal Date: December 30, 2009

Inspection Summary Goal Date: October 30, 2009

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects [Number BL>WL]	Indication
Site 008 Leonard Gomella, MD Department of Urology Jefferson Medical College, Suite 1102 1025 Walnut Street Philadelphia, PA 19107	PC B305/04	8 [6 B L > WL]	Sites with highest number and percentage of additional patients detected by Blue-light and not by white-light cystoscopy [75%]
Site 010 Edward M. Messing, MD University of Rochester Medical Center Department of Urology 601 Elmwood Avenue, #656 Rochester, New York 14642	PC B305/04	11 [4 BL > WL]	Sites with highest number and percentage of additional patients detected by Blue-light and not by white-light cystoscopy [36%]
Site 403 T.M. de Reijke Academic Medical Center (AMC) Department of Urology Meibergdreef 9 1105 AZ Amsterdam The Netherlands	PC B305/04	12 [5 BL > WL]	Sites with highest number and percentage of additional patients detected by Blue-light and not by white-light cystoscopy [42%]

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

For Study PC B305/04, 27 Study Centers were utilized. Among the Hexvix pre-treated group, 278 patients had Ta or T1 papillary bladder tumors according to consensus pathology assessment and in 47 patients at least one additional Ta or T1 tumor was detected by blue light and not detected by white light. Review of these Clinical Sites for this Study revealed that those Centers with the largest number of patients detected as having at least one Ta or T1 lesion according to consensus pathology assessment yielded the fewest number of additional Ta or T1 lesions detected by blue light. In contrast, those sites where at least one Ta or T1 was detected by blue light and not detected by white light were observed at sites with smaller numbers of patients with Ta or T1 tumors. The Table that follows summarizes these data. Therefore, we have selected the three centers for inspection with the highest numbers and percentages of patients with additional Ta or T1 lesions detected by blue light and not by white light (**shown in RED text**).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Study PC B305/04

Summary Evaluation of Centers with Largest Number of Hexvix Group Patients with Ta or T1 Papillary Tumors and Largest Number of Patients BL>WL Ta or T1 Papillary Tumors

Number Patients Ta or T1	Number Patients BL>WL	Study Centers N = 28	Center Locations	Number Patients BL>WL	Number Patients Ta or T1
Sites with Largest Number of Ta or T1 Patients Number in Hexvix Group with Ta or T1 Lesions = 278					
30	1 (3%)	304	Germany		
26	0 (0%)	201	Canada		
23	5 (22%)	11	Rochester		
23	2 (9%)	301	Germany		
23	2 (9%)	302	Germany		
BL>WL Patients	10/47 (21%)				
Sites with Largest Number of BL>WL Patients Number of BL>WL Ta or T1 Patients = 47					
8	Philadelphia	6 (75%)	8		
11	Rochester	5 (22%)	23		
16	Miami	5 (26%)	19		
403	Netherlands	5 (42%)	12		
10	Rochester	4 (36%)	11		
402	Netherlands	4 (29%)	14		
		29/47 (62%)	BL>WL Patients		

Should you require any additional information, please contact Trinh Scott, RPM at 301-796-3311 or Scheldon Kress, M.D. at 301-796-1391. Dr. Scheldon Kress would be interested in accompanying the inspector to one of these clinical site inspections.

Concurrence: (as needed)

Scheldon Kress, M.D., Medical Reviewer
Alexander Gorovets, M.D., PhD., Medical Team Leader
Rafel Dwaine Rieves, M.D., Division Director (for foreign inspection requests or requests
for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results? Yes*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites? Yes*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites? No*
- *Are there concerns that the data may be fraudulent or inconsistent? No*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct? No*
- *Is this a new molecular entity or original biological product? Yes*
- *Is the data gathered solely from foreign sites? No*
- *Were the NDA studies conducted under an IND? Yes IND 51224*

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009