CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022555Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 25, 2010
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-555 Response to Complete Review letter of 12/30/09
Applicant Name	Photocure ASA
Date of Submission	March 31, 2010
PDUFA Goal Date	June 1, 2010
Proprietary Name / **Established (USAN) Name**	Cysview Hexaminolevulinate Hydrochloride for Intravesical Solution
Dosage Forms / Strength	Supplied as a "kit" of three components: -10 mL glass vial containing a powder presentation of 100 mg hexaminolevulinate hydrochloride -50 mL polypropylene vial containing a "Solvent for Hexvix" (phosphate buffer) - one luer Lock catheter adapter (to connect the syringe containing Cysview to a urethral catheter)
Proposed Indication(s)	"Cysview is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1)."
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Scheldon Kress, MD
Statistical Review	Anthony Mucci, PhD
Pharmacology Toxicology Review	Yanli Ouyang, MD, PhD
CMC Review/OBP Review	Ravindra Kasliwal, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Christy John, PhD
DDMAC	Michelle Safarik, PA-C
DSI	Susan Thompson, MD
CDTL Review	Alexander Gorovets, MD
OSE/DMEPA	Anne Crandall, PharmD
OSE/DDRE	not performed/not applicable; no REMS
OSE/DRISK	not performed/not applicable; no REMS
CDRH/Device Review	Mary J. Cornelius/Joshua Pfefer, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Cysview is the (FDA-accepted) trade name for hexaminolevulinate hydrochloride, a porphyrin precursor, that is purportedly transformed within cells into a photosensitive compound. Specifically, the applicant proposes that the administration of Cysview to the bladder mucosa results in preferential concentration of the drug within neoplastic urothelium. Subsequent visualization of the bladder mucosa with a special type of cystoscope (a “blue light”) allows the detection of the pink-red fluorescent tissue, a marker of the photosensitive porphyrin accumulation. Hence, fluorescence of bladder mucosa following Cysview administration is reportedly a marker for the location of neoplastic tissue.

Cysview has been developed as a "combination product" because a special cystoscope must be used concomitantly with the drug. This cystoscope is the subject of a PMA currently under review by the CDRH. We have been informed that the CDRH review team is currently targeting approval of the PMA on May 28, 2010 (to coincide with our targeted approval of the NDA).

Cysview was not classified as a “new molecule” based upon the prior FDA approval of sufficiently similar porphyrin precursors. Consequently, this NDA was assigned a division-level signatory authorization.

This March 31, 2010 submission is a response to an original cycle Complete Response (CR) letter issued on December 30, 2009. The major regulatory issues cited within the CR letter pertained to:

1) On-going review of the investigational cystoscope (if approved, both the drug and device would need approval at the same time/of particular concern was unresolved device facility inspectional issues);

2) Insufficient labeling and usage information, particularly description of the reconstitution, administration and cystoscopic examination procedures (the supplied proposal was excessively conducive to medication errors and failed to provide essential logistical information).

Cysview (which was called “Hexvix” at one time) was discussed at a December 17, 2009 Oncologic Drugs Advisory Committee where members voted 9 to 8 in response to a question that asked, "do the data establish a favorable diagnostic benefit/risk assessment?"

The current submission (March 31, 2010) contained revised labeling that was intended to address the CR letter expectations. At the time of submission, the applicant indicated that all PMA inspectional issues had been resolved. During this review cycle, the only review team

issues pertained to the development of acceptable package insert text and carton/container labeling. All of these issues were resolved.

2. Background

The applicant's clinical development program for Cysview originally focused upon two target indications:

-detection of carcinoma in situ (CIS)
-detection of non-muscle invasive papillary bladder cancer

The clinical development program for the CIS indication was completed prior to the papillary cancer program. Consequently, an NDA for the CIS detection was submitted to the FDA in 2005. FDA's review assessed deficiencies in the major clinical studies, mainly due to the inability to verify the thoroughness of white light cystoscopy (a comparator for the blue light results) and inconsistencies in pathologic diagnoses (particularly between local sites and central facilities). FDA requested additional clinical data to verify the drug's diagnostic efficacy for the CIS indication.

In 2009, the applicant submitted a second NDA; this new application pertained to the papillary cancer indication. In support of this indication, the applicant submitted data from a single major phase 3 clinical study (Study 305) as the confirmatory evidence of the drug's diagnostic efficacy and safety.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The reconstitution procedures were simplified and the proposed labeling revised to minimize the potential for medication errors.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

I have examined the clinical and statistical reviews and generally concur with the observations. Of note, no new clinical data were submitted with this March, 2010 submission. The main confirmatory clinical data are derived from Study 305 (a single study) and were reviewed in the original review cycle. Multiple other studies provided exploratory information. The totality of data, including medical practice considerations were considered. Our summary findings support a favorable risk to benefit consideration based upon all the data/with this determination based upon the proposed "detection" indication. (b) (4) Note that Cysview was initially called “Hexvix” and the following description refers to “Hexvix,” consistent with the original cycle nomenclature.

In Study 305, approximately 800 adult patients with known or suspected bladder cancer (based upon prior cystoscopic findings) were randomized to either the “white light group” (white light only) or the “Hexvix group” (white light followed by blue light). Following completion of the cystoscopy, patients with pathologically confirmed Ta or T1 lesions underwent follow-up white light cystoscopies at 3, 6 and 9 months.

A special protocol assessment for study 305 was submitted to the FDA in 2003. FDA’s Division of Reproductive and Urologic Products provided advice regarding the design of this study with the understanding that the sponsor intended data from this single study to confirm efficacy and safety. For example, FDA requested the sponsor to develop the analytical plan to provide strong statistical persuasiveness for the co-primary endpoint results. In response, the final study protocol designated statistical success for each co-primary endpoint as a p-value of less than 0.01. Additionally, the sponsor addressed concerns related to the thoroughness of white light cystoscopy by incorporating a special “re-randomization” procedure within the study design. This procedure was intended to provide an incentive for site urologists to thoroughly examine the bladder under white light within the Hexvix group (since a portion of the patients in this group could have been randomized to no blue light cystoscopy).

Using the prespecified analytical criteria, Study 305 achieved success upon one of the study’s co-primary endpoints. Specifically, the proportion of Hexvix group patients who had a Ta or T1 lesion detected only with blue light (16%) exceeded the prespecified 10% threshold ($P < 0.01$). However, this desired level of statistical success was not achieved for the study’s second co-primary endpoint. This endpoint was a “superiority” comparison of the follow-up “recurrence rate” between the Hexvix group and the white light group. The results showed a “recurrence” rate of 47% in the Hexvix group and 56% in the white light group ($P = 0.03$).

Four supportive clinical studies obtained Ta and T1 bladder cancer detection data although the studies were designed primarily for other purposes. These studies contained several limitations (such as inability to verify the thoroughness of white light cystoscopy and

limitations in pathology assessments) but did allow post-hoc analyses of Ta and T1 bladder cancer detection outcomes. These exploratory analyses favored the diagnostic efficacy of Hexvix.

One supportive study (Study 304) compared "recurrence" rates between patients randomized to white light or Hexvix. The study did not show a reduction in recurrence for the Hexvix group.

Overall, the "detection" data emphasize the importance of a thorough white light examination since some lesions (particularly high grade lesions) were missed with Hexvix/blue light. This importance was an important consideration for labeling.

8. Safety

No major safety concerns were evidenced in clinical studies although post-marketing experience has suggested a risk for hypersensitivity/anaphylaxis reactions. Hexvix (now known as Cysview) has been administered to approximately 57,000 patients since its European marketing approval in 2005 (Sweden in 2004). In this post-marketing experience, three patients have experienced hypersensitivity/anaphylaxis reactions potentially related to Hexvix/Cysview. One of these patients reportedly had a “positive” skin test to Hexvix/Cysview.

Potential Hexvix/Cysview safety concerns also relate to the possibility of misdiagnosis (i.e., surgical complications related to biopsy of “false positive” blue light lesions) and uncertainty regarding the frequency with which Hexvix/Cysview can safely be re-administered to a patient. In the clinical studies, patients underwent a single Hexvix administration. In clinical practice, physicians may wish to consider Hexvix administrations as a component of periodic follow-up cystoscopy. The safety of repetitive Hexvix administrations has not been assessed; this is an important consideration for labeling and was the basis for a post-marketing committement.

9. Advisory Committee Meeting

As noted above, an advisory committee voted 9 to 8 in favor of a sufficient risk to benefit consideration for Hexvix/Cysview.

10. Pediatrics

Pediatric studies were waived; the condition is rare to non-existent in pediatric patients.

11. Other Relevant Regulatory Issues

DSI inspections determined the Study 305 data maintained acceptable integrity.

12. Labeling

Labeling had been developed in an acceptable manner and the text accurately describes the study results/drug usage recommendations.

13. Decision/Action/Risk Benefit Assessment

Overall, I concur with the review team's recommendation for approval. The following two post-marketing commitments address the CIS and repetitive administration concerns:

1642-1 A prospective, randomized, controlled clinical study that will assess the safety and efficacy of repetitive use of Cysview in the detection of bladder cancer.

Final Protocol Submission: May 2011
Study/Trial Completion: July 2015
Final Report Submission: July 2015

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.

Final Protocol Submission: May 2011
Study/Trial Completion: July 2015
Final Report Submission: July 2015

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/

RAFEL D RIEVES
05/25/2010