

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022555Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review (NDA 22-555)

NDA	22-555	Submission Date	March 31, 2010
Brand Name	Hexaminolevulinate Hydrochloride		
Generic Name	Cysview		
Reviewer	Christy S. John, Ph.D		
Team Leader	Young Moon Choi, Ph.D.		
OCP Division	V		
ORM Division	Division of Medical Imaging		
Sponsor	Photocure ASA, Cato Research Ltd. 4364 S. Alston Ave. Durham, NC 27113		
Relevant IND(s)	51,224		
Submission Type; Code	Resubmission		
Formulation; Strength(s)	100 mg		
Indication	Cysview is an optical imaging agent indicated for use with photodynamic blue light cystoscopy performed with Karl Storz D-Light C Photodynamic Diagnostic (PDD) system, in which cystoscopy in the blue light setting (Mode 2) is performed as an adjunct to cystoscopy in the white light setting (Mode 1), for the detection of non-muscle invasive papillary cancer of the bladder in patients undergoing cystoscopic surgery for with known or suspected, initial or recurrent bladder cancer.		
Proposed Dose	The recommended dose for adults is 50 mL of reconstituted solution of Cysview (100 mg), instilled into the bladder via urinary catheter.		

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1. Executive Summary

An Original NDA (b) (4) was submitted by the applicant for (b) (4) for the detection of carcinoma in situ in bladder cancer patients. The Agency issued a non-approval letter on April 19, 2006.

The applicant had re-submitted a New Drug Application (NDA 22-555, Type 505(b)1, in response to Agency's Complete Response Letter for Cysview (old name Hexvix), a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz PDD system, as an adjunct to white light cystoscopy in the detection of no-muscle invasive papillary cancer of the bladder.

There were no clinical pharmacology deficiencies in the original submission and no new clinical pharmacology information has been submitted in the present resubmission to NDA 22-555. However, the sponsor's proposed labeling was reviewed and the labeling should be revised as recommended.

1.1. Recommendations:

We recommend that the package insert be modified as indicated in the Detailed Labeling Recommendations section of this review.

1.2 Summary of Clinical Pharmacology Findings:

This NDA provides evidence that Cysview photodynamic blue light cystoscopy in conjunction with white light cystoscopy improves detection of papillary tumors (Ta and T1 stage) in bladder cancer patients compared with white light cystoscopy alone. The diagnostic efficacy of Cysview cystoscopy was demonstrated by a multi-national pivotal Phase 3 clinical study conducted under IND 51,224, Study PC B305/04, which comprised of 814 enrolled subjects. Study PC B305/04 was designed to be a single stand-alone study. In addition, the evidence of improved detection of papillary tumors with Cysview was provided by 4 Phase 3 studies: PC B304/04, a new, 2-center study which comprised of 233 enrolled subjects and was conducted in Denmark; and Studies PC B301/01, PC B302/01, and PC B303/01, studies previously submitted to Hexvix NDA (b) (4).

There are no additional clinical pharmacology studies over the previous submission (b) (4). This review regards on the new package insert.

2. Detailed Labeling Recommendations

The applicant's proposed PLR format package insert is reproduced, together with the FDA Reviewer's edits under section 3 of the present review. The recommendations from clinical pharmacology perspectives are incorporated in Section 7 and Section 12 of the label as below:

Section 7. The following change should be made:

DRUG INTERACTIONS

No specific drug interaction studies have been performed.

Section 12. The following language should be inserted:

12.1 Mechanism of Action

(b) (4)

12.2 Pharmacodynamics

In vitro studies have shown increased porphyrin fluorescence in normal urothelium after exposure to Cysview. In the human bladder, a greater accumulation of porphyrins is proposed in neoplastic or inflamed cells, compared to normal urothelium. After bladder instillation of Cysview for approximately 1 hour and subsequent illumination with blue light at wavelengths (b) (4) – 450 nm [see Dosage and Administration (2.3)], the porphyrins will fluoresce red.

12.3 Pharmacokinetics

After bladder instillation of [¹⁴C]-labeled Cysview (100 mg) for approximately 1 hour in healthy volunteers, the absolute bioavailability of Cysview was 7% (90% confidence interval [CI]: 5%-10%). The [¹⁴C]-labeled substance(s) showed biphasic elimination, with an initial elimination half-life of 39 minutes, followed by a terminal half-life of approximately 76 hours. Whole blood analysis showed no evidence of significant binding of Cysview to erythrocytes. An in vitro study showed that Cysview underwent rapid metabolism in human blood.

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

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/

CHRISTY S JOHN
05/11/2010

YOUNG M CHOI
05/12/2010
I concur.

NDA	22-555	Submission Date	June 30, 2009
Brand Name	Hexvix™		
Generic Name	Hexvix™		
Reviewer	Christy S. John, Ph.D		
Team Leader	Young Moon Choi, Ph.D.		
OCP Division	V		
ORM Division	Division of Medical Imaging and Hematology Drug Products		
Sponsor	PHOTOCURE ASA C/O CATO RESEARCH WESTPARK CORPORATE CENTER 4364 SOUTH ALSTON AVE DURHAM, NC 27713		
Relevant IND(s)	51,224		
Submission Type; Code	Priority : P	Original:1	
Formulation; Strength(s)	Hexvix for Intravesical Solution 100 mg is supplied with diluent for Hexvix, 50 mL in polypropylene or clear glass vial.		
Indication	Hexvix 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.		
Proposed Dose	100 mg (50 ml of 2mg/ml solution for 1 hour instillation in the bladder)		

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1. EXECUTIVE SUMMARY

Investigational New Drug Application (IND) 51,224 for Hexvix was submitted on 29 October 2001 in combination with Karl Storz Photodynamic Diagnosis (PDD) system for the detection of superficial bladder cancer. NDA (b) (4) for Hexvix was filed by the applicant on June 30, 2005 for the indication of detection of carcinoma in situ lesions in bladder cancer patients. The Agency issued a Complete Response letter with deficiencies mostly related to “verifiable evidence of efficacy”. NDA (b) (4) was found to be “acceptable” from clinical pharmacology perspective. There were no clinical pharmacology comments/deficiencies.

The applicant conducted additional Phase 3 study (PC B304/04) as a part of Special Protocol Assessment in consultation FDA and filed a new NDA 22-555 on June 30, 2009. This application provided evidence that Hexvix photodynamic blue light cystoscopy (Hexvix cystoscopy) in conjunction with white light cystoscopy improves the detection of papillary tumors (Ta and T1 stage) in bladder cancer patients compared with white light cystoscopy alone.

There are no additional clinical pharmacology studies in NDA 22-555. Therefore, most of the review for NDA 22-555 remains the same (b) (4). The clinical pharmacology section of the label has been reviewed and the edits have been suggested.

1.1 RECOMMENDATIONS:

The Office of Clinical pharmacology, Division of Clinical Pharmacology V has reviewed the current submission, NDA 22-555 and found that it is acceptable from clinical pharmacology perspectives provided the applicant and Agency come to a mutual agreement on proposed labeling changes. Labeling recommendations have been made in clinical pharmacology section of the label (Refer to the page 11 of this review).

1.2 PHASE 4 COMMITMENTS:

None

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS:

Diagnosis of bladder cancer is commonly confirmed by urinalysis, urine cytology, flow cytometry, sonography, and cystoscopic examination including biopsy. Macroscopic tumors including non-invasive papillary tumors in the bladder are relatively easy to visualize by standard cystoscopic examination under white light. However, dysplasia and carcinoma in situ (CIS) are easily overlooked. The present recurrence rate of 50%-70% shows the inadequacy of white light cystoscopy for detection and resection of lesion of bladder.

Fluorescence cystoscopy is a technique currently under clinical development for the visualization of malignant and pre-malignant lesions. Photodetection is achieved by the preferential enrichment in neoplastic tissue of photoactive protoporphyrins (PAP) that fluoresce under light of an appropriate wavelength. The intravesical administration of 5-aminolevulinic acid (5-ALA) to stimulate the formation of PAP has been investigated for detection of neoplastic lesions in the bladder. The major drawback of 5-ALA is its hydrophilic properties that may limit its ability to penetrate tumor tissue. A solution to this problem is the administration of 5-ALA derivatives with more lipophilic characteristics that would allow better absorption and, thus, formation of more PAP at the site of action.

The applicant has developed Hexvix for blue light cystoscopy as an adjunct to white light cystoscopy in the detection of carcinoma in situ (CIS) of the bladder in patients with known or suspected superficial bladder cancer. Hexvix blue light cystoscopy is NOT intended to replace random biopsies or other procedures required to assure adequate tumor detection at cystoscopic examination. Hexvix is an ester of the endogenous early precursor, ALA in the biosynthesis of heme.

Hexaminolevulinate is the precursor of a selective photosensitizer which when applied exogenously, leads to the formation of PAP which accumulates in malignant and premalignant tissue, in part due to altered enzymatic activity in neoplastic tissue. Photodetection is achieved by the preferential enrichment in neoplastic tissue of PAP that fluoresces under illumination with blue light of an appropriate wavelength.

The drug is supplied as a kit with 2 components: The powder contains 100 mg hexaminolevulinate hydrochloride, corresponding to 85 mg of the active moiety HAL. Dissolution in 50 mL Solvent for Hexvix provides an 8 mM (1.7 mg/mL) solution of HAL for intravesical instillation. Following a 1-hour exposure time to allow formation of sufficient levels of photoactive protoporphyrins (PAP), followed by bladder evacuation, then the patient undergoes cystoscopy. Hexvix induces the formation of PAP in malignant and premalignant cells in the urothelium when instilled in the bladder.

In the human pharmacokinetic section of the present submission the sponsor provided the results of one pharmacokinetic (PK) study (absolute bioavailability) and in-vitro stability in human blood and urine. HAL was found to be unstable in human plasma and in whole blood under all storage conditions. After incubation for 30 and 60 minutes in human plasma and in whole blood at room temperature, only 65 and 21% was recovered respectively. It is therefore implied that an extensive degradation of HAL would take place in human blood after any systemic uptake following intravesical administration in the bladder.

One PK study (PC B103/03) was conducted to determine the absolute bioavailability using C-14 labeled Hexvix. The systemic exposure to HAL hydrochloride after intravesical administration for one hour to healthy volunteers was low, with a mean bioavailability of 7% and a 90% confidence interval of 5-10%.

Analysis of the data available from patients exposed for 2 hours to different Hexvix concentrations indicated a strong concentration dependence on the PpIX fluorescence. It appeared that within 2 hr, a solution of 8 mM Hexvix generated the highest fluorescence levels as compared to 4 mM and 16 mM of Hexvix. An increase of fluorescence intensity with instillation time was observed. From this study it was concluded that a 2 hour instillation and 2 hour resting gave the maximum fluorescence and thereby would be optimum time for imaging. However, in the clinical trials cystoscopy was performed after one hour.

Due to the unique route of administration and a low systemic uptake, no formal drug-drug interaction and no organ (hepatic or renal) dysfunction studies were conducted.

The applicant did not conduct formal drug-drug interaction studies. However, in Phase 2 and 3 studies, no apparent drug-drug or drug-disease interactions were observed with Hexvix administration. Hematuria (red blood cells in urine) was the most frequently reported AE in both gender groups.

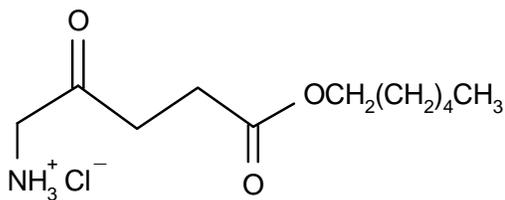
It should be noted, that Karl Storz Photodynamic Diagnostic Device (PDD) system has been used in the clinical studies with Hexvix and consists of a rigid Hopkins® II telescope with a camera system. This PDD system is not approved for use in the US but the pre-market approval application has been submitted in parallel to this submission. CDRH is currently reviewing this submission.

2. Question-Based Review:

2.1 General Attributes:

What are the general attributes of Hexvix?

The chemical name of Hexvix is hexyl aminolevulinate hydrochloride, the United States Adopted Name (USAN) is hexaminolevulinate hydrochloride. The structural formula is shown below.



Hexyl aminolevulinate hydrochloride is a white to slightly yellow powder,

(b) (4)

How is the drug product formulated? Are there any issues with formulation?

The Hexvix formulation is composed of Hexvix powder containing 100 mg of hexaminolevulinate hydrochloride, corresponding to 85 mg of the active moiety HAL. Hexvix Powder is dissolved in 50 mL Solvent for Hexvix, a sterile (b) (4) resulting in a final pH of the solution of approximately 6 (specification range, pH 5.7 to 6.2). Dissolution in 50 mL Solvent for Hexvix provides an 8 mM (1.7 mg/mL) solution of HAL for intravesical instillation.

(b) (4)

What is the proposed mechanism of action of Hexvix?

Hexaminolevulinate (hexyl aminolevulinate) (HAL) is an ester of the endogenous early precursor in the biosynthesis of heme, 5-aminolevulinic acid (ALA). The heme synthesis pathway is regulated by the amount of heme in the cell, resulting in inhibitory action on the synthesis of ALA. This regulation can be overruled by supplying exogenous ALA or derivatives

such as HAL. Protoporphyrin IX (PpIX), an endogenous photosensitizer, is the last intermediate in the synthesis of heme in humans. Since the formation of heme from PpIX is tightly regulated, the administration of HAL will lead to the accumulation of PpIX and other PAP.

(b) (4)

What is the proposed dosage and route of administration of Hexvix?

The Hexvix formulation (100 mg powder dissolved in 50 mL phosphate buffered saline) will be used for intravesical instillation via a catheter. Following a 1-hour exposure time to allow formation of sufficient levels of PAP, followed by bladder evacuation, the patient can undergo cystoscopy. In all three phase 3 clinical trials, Hexvix 8 mM solution (50 mL) was instilled into the bladder via catheterization and retained for 1 hour. Following voiding, all protocols called for the initiation of anesthesia and white light cystoscopic examination in conjunction with blue light illumination within thirty minutes. White light cystoscopy and fluorescence (blue light) cystoscopy are then performed in the same procedure. For this combined examination, the devices used for white light cystoscopy are modified to include additional filters allowing examination with both white and blue light. The Karl Storz Photodynamic Diagnostic Devices (PDD) system has been used in the clinical studies with Hexvix and consists of a rigid Hopkins® II telescope with a camera system. This PDD system has been safely used in the European Union since 1995. This PDD system is not approved for use in the US but the pre-market approval application has been submitted along with this application and is being reviewed by CDRH as well.

2.2 General Clinical Pharmacology:

What are the design features of the clinical pharmacology studies to support dosing or claim?

In the present submission, the sponsor provided results from 1) in vitro stability in human plasma and urine 2) one absolute bioavailability study and 3) three pharmacodynamic studies correlating various doses and incubation (resting) time in bladder vs emitted fluorescence.

Are there any active moieties in the plasma (or any other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Hexvix is administered locally at the site of tumor via a catheter (inside bladder). The sponsor has not attempted to characterize any metabolites. There are no active moieties in the plasma or any other biological fluid to assess pharmacokinetic parameters and exposure response relationship.

Is the drug formulation stable in urine (bladder) and blood?

HAL was found to be unstable in human plasma and in whole blood under all storage conditions (after incubation for 30 and 60 minutes at room temperature, only 65 and 21% respectively, was recovered). It is therefore implied that an

extensive degradation of HAL would take place in human blood after any systemic uptake following intravesical administration in the bladder. A study was performed to determine the stability of P-1206 (Hexvix) in vitro following incubation with human urine at 37°C. During instillation in the bladder, P-1206 will be diluted by urine and it may decompose. Urine samples from 3 male and 3 female volunteers were collected individually. A nominal concentration of 1.0 mg P-1206/mL was used and incubated at 37°C for 2 hours. It was found that P-1206 appeared stable over the experimental period; there was very little variation in concentration between replicates of urine at each time point; and there was no obvious difference in the concentration of P-1206 between male urine, female urine, or buffer control samples.

What is the rationale for dose justification? How is dose-response relationship established? How is optimum imaging time determined?

In vivo study in patients, solutions of ALA and HAL were instilled into the bladder of 18 patients presenting with recurrent bladder cancer. The accumulation and distribution of PpIX after instillation of HAL 8 mM for 2 and 4 hours in patients with recurring bladder cancer. The distribution of PpIX through the bladder wall was studied in frozen biopsies using fluorescence microscopy and correlated with pathological findings. Patients were divided in 2 groups and stratified according to previous treatment, histology, and current diagnosis. Six patients received a 50-mL intravesical instillation of HAL 8 mM for 2 hours (including a 2-hour rest before cystoscopy, 2+2-hour regimen), while the other group of 6 patients received an instillation of HAL 8 mM for 4 hours with no rest before cystoscopy. Bladder cystoscopy was performed under spinal or general anesthesia and by using the D-light system (Karl Storz, Tuttlingen, Germany), the bladder was inspected under blue light (fluorescence). Biopsies were obtained from frozen tumors and analyzed using a fluorescence microscope.

Bladder instillation of 50 mL HAL 8 mM resulted in no reports of adverse reactions. Microspectrofluorometry of the samples showed significant increase of PpIX fluorescence in all tumor samples compared with biopsies from normal urothelium. The 2+2-hour instillation regimen provided higher PpIX levels compared with the 4-hour instillation time and was more than 8 times higher compared to autofluorescence from normal tissue. The PpIX concentration was high in the urothelium, but low in the lamina propria, and not measurable in the muscle for both dose regimens. The study showed that by instilling 50 mL of HAL 8 mM into the bladder, a preferential enrichment in cancerous cells of PAP was obtained. The distribution of fluorescence was homogeneous in all parts of the tumor. Outside the urothelium, only small amounts of fluorescence in the connective tissue were observed. These results, supported by the lack of adverse events, indicated a low systemic uptake of HAL.

The distribution of protoporphyrin IX (PpIX) through the bladder wall was studied on frozen biopsies using fluorescence microscopy and correlated with pathological findings. The usefulness of fluorescence cystoscopy relies on the selective accumulation of PAP in malignant tissue. To investigate the pharmacokinetics of the main porphyrin, the accumulation and distribution of PpIX in human and porcine bladder mucosae was studied by micro-spectrofluorometry. Pig and human urothelium have very similar structure, which was reflected in the PpIX accumulation.

The accumulation of PpIX after a 1-hour incubation using different HAL concentrations suggested a bell-shaped dose-response curve with the optimal concentration in the range of 2 to 10 mM. Using an optimal concentration, HAL showed a linear dose-response (PpIX intensity) between 1 and 5 hours of incubation of pig mucosae. With longer incubation, the dose response leveled off, suggesting a saturation of the biosynthetic pathway for the production of PpIX. A tissue preparation stained with acridine orange after 7 hours of incubation resulting in maximum accumulation of PpIX concentration showed nuclear fluorescence, indicating that the cells were alive with an intact metabolic function. The fluorescence profiles across the mucosae were recorded after incubation with HAL for 2 hours. The fluorescence showed a high peak in the urothelium, which sharply decreased in the underlying connective tissue, indicating low bioavailability of HAL in connective tissue and fat.

Analysis of the data available from patients exposed for 2 h (patient nos. 1, 2, 5, 6, 7, 20, and 21) to different Hexvix concentration indicated a strong concentration dependence on the PpIX fluorescence. It appeared that, within 2 hr, a solution of 8 mM Hexvix generated the highest fluorescence levels as compared to 4 mM and 16 mM of Hexvix. An increase of fluorescence intensity with instillation time was observed. In addition, taking both the total fluorescence and the slope of the graphs into consideration, it was shown that an instillation of 8 mM Hexvix solution is more efficient than that of 4 mM.

This study was designed to evaluate the intensity and localization of PpIX in malignant and nonmalignant cells of the human bladder following topical administration of ALA or HAL. Solutions of ALA (180 mM) or HAL (8 mM) were instilled into the bladders of 18 patients with recurrent TCC. The distribution of PpIX through the bladder wall was studied on frozen biopsies using fluorescence microscopy and correlated with pathological findings.

Topical bladder instillation with 180 mM (3%) ALA administered for 6 hours or 8 mM (0.2%) HAL administered for 4 hours gave similar results regarding intensity and tissue distribution of PpIX fluorescence, whereas 8 mM HAL administered for 2 hours followed by 2 hours of resting time (2+2 hours concept) induced a PpIX fluorescence twice as high. The

fluorescence remained limited to cancer cells. Only a trace of PpIX fluorescence was observed in suburothelial connective tissue (chorion) but none in the bladder smooth muscle regardless of experimental conditions. In conclusion, HAL is an excellent precursor for PpIX synthesis in bladder cancer. With the 2+2 hour topical administration condition, it yielded the highest PpIX fluorescence intensity and fluorescence contrast between normal and malignant urothelial cells.

However, the sponsor has used only 1 hour instillation and less than 30 minutes rest before imaging studies. Therefore, the images obtained may not be the "optimal images" that one could possibly obtain and thereby affecting the eventual clinical efficacy.

Table I. The *in vivo* correlation of exposure (concentration) vs. response (fluorescence signal).

Patient no.	Concentration (mM)	Instillation time (h)	Resting time (h)	Fluorescence signal (r.u.)
1	4	2	–	16.2
2	4	2	–	11.2
3	4	4	–	34.5
4	4	4	–	20.5
5 ^b	8	2	–	22.1
				38.4
6	8	2	–	36.2
7	8	2	–	46.7
8	8	2	–	–
9 ^b	8	2	2	151.1
				102.0
10	8	2	2	115.8
11	8	2	2	147.5
12	8	4	–	66.4
13	8	4	–	72.6
14	8	4	–	63.4
15	8	4	–	73.8
16	8	4	–	94.4
17	8	4	–	77.1
18	8	4	2	102.7
19	8	4	2	95.0
20	16	2	–	15.8
21	16	2	–	16.7
22	180 ^a	4	2	54.0
23	180 ^a	4	2	43.6
24	180 ^a	4	2	46.2
25	180 ^a	4	2	45.3

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^aInstillation of the 180 mM solution of ALA. ^bPatient with two papillary tumours.

In another study, twenty-five patients (7 women and 18 men, 4 cases of ordinary ALA and 21 cases of Hexvix) were involved in a study. The mean age was 70 years, covering an age range 44-85. 50-200 mg (4-16 mM of crystalline h-ALA) were dissolved in 35 mL of water. Then 13 ml of PBS were added to the aqueous solution and adjusted with 0.1 hydrochloride to give a pH value of 5.3. The solution was instilled into patients' bladder using a 16 French Foley catheter. The patients were asked to retain the solution for 4 h. Their bladders were evacuated 2 h prior to treatment. Prior to further treatment or measurement, the actual status of the bladder was documented under white light illumination. The frame accumulation color CCD camera (Storz, Tuttlingen, Germany), connected to a video recorder (JVC Japan) and a RGB monitor (Sony, Japan) was plugged directly into the ocular of a 23.5 French cystoscope (Storz PDD, Tuttlingen, Germany) to record the standard endoscopic color image. Fluorescence emission spectra were recorded with an optical

fibre-based spectrofluorometer based on a Peltier cooled CCD (Charge Couple Device) coupled to a spectrograph (Cromex 250, SI Instruments, Germany).

The results showed that all aqueous solutions of HAL stayed clear and colorless until use. Neither systemic nor local reaction following examination with both Hexvix and ALA were observed under the conditions used in this study. Even the highest drug dose 16 mM of Hexvix was well tolerated. Hexvix induced synthesis of PpIX was observed in each patient.

Does this drug prolong QT or QTc?

The drug is present in a very low amount in systemic circulation and administered locally only once, the sponsor did not study the QT or QTc interval prolongation.

2.3 Intrinsic Factors:

Q. What intrinsic factors (age, gender, race, weight, height, genetic polymorphism, and organ dysfunction) influence PK and response, and what is the impact of any difference in exposure on efficacy or safety response?

No organ (hepatic or renal) dysfunction studies were conducted due to local application of the drug.

The small number of non-Caucasians (26) in the controlled studies precluded analyses based on race. The subgroup safety discussion therefore only covers males versus females and patients younger than 65 years old versus patients 65 years and older. However, men 65 years and older comprised the majority of patients in the studies and the results for the 65-years-and-older and the male subgroups generally reflected the overall study results. The ratios of male to females and patients 65 years and older to patients younger than 65 years old were approximately 3 to 1 and 2 to 1, respectively. There were no important differences or trends in the incidence, frequency, and severity of AEs among the male and female patients and the overall patient population. As with the overall population, hematuria was the most frequently reported AE in both gender groups, with comparable incidences following Hexvix instillation. Following hematuria, dysuria and post-procedural pain were the most frequently reported events in both groups.

The AE incidence in men mirrored essentially that of the overall population. The incidence of renal and urinary disorders tended to be slightly lower in female patients (31.0%) than in male patients (38.2%) and the overall population (36.5%). In contrast, a slightly higher incidence of nausea, headache, pubic pain, and hypertension was noted in female patients compared with males.

2.4 Extrinsic Factors:

Q. What extrinsic factors (drugs) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

Due to unique route of administration and a low systemic uptake, no formal drug-drug interaction studies were conducted. Based on the generally aged population participating in the Phase II and Phase III studies and the indication of Hexvix cystoscopy, patients with multiple concomitant medications and disease states were enrolled.

Nearly all patients who received Hexvix received concomitant medications, while all patients undergoing cystoscopy received concomitant medications. Most of these medications were consistent with an older population with a malignant disease and with the cystoscopic procedure. The most common concomitant medications, propofol, midazolam, paracetamol, and other anesthetics and sedatives administered reflect the frequent use of medication during the cystoscopy procedure.

No apparent drug-drug or drug-disease interactions were observed with Hexvix administration. Based on the limited systemic uptake of Hexvix and the instability in human blood, any potentially interfering pharmacokinetic interactions with other drugs would not be predicted.

2.5 General Biopharmaceutics

What is the absolute bioavailability of the proposed to-be-marketed formulation?

Hexvix is supplied as a freeze dried powdered to be dissolved in 50 mL solvent and to be instilled in bladder via a catheter. After one hour of instillation the bladder would be emptied and cystoscopy to be performed. The relative systemic bioavailability following single-dose intra-vesical (100 mg) and intravenous (0.15 mg/kg) administration of [¹⁴C]-labeled HAL hydrochloride was investigated in an open-label, 2-period study in 8 healthy male volunteers (Study PC B103/03, details given in Appendix).

The systemic exposure to HAL hydrochloride after intravesical administration for one hour to healthy volunteer was low, with a mean bioavailability of 7% and a 90% confidence interval of 5-10%.

2.6 What analytical method was used to determine hexvix in whole blood and plasma?

Plasma and whole blood samples were analyzed (b) (4). Samples of drug preparation and Hexvix solution after bladder evacuation, were analyzed (b) (4). To measure the ¹⁴C-content (b) (4) of blood, plasma and urine samples obtained from subjects administered an intravesicular and an intravenous dose of C-HAL. (b) (4)

(b) (4)

3. Detailed labeling recommendations:

The clinical pharmacology section of the package insert has been modified to read as follows:

(b) (4)



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4.2 INDIVIDUAL STUDY REVIEW

PK STUDY (PC B103/03) TO DETERMINE BIOAVAILABILITY:

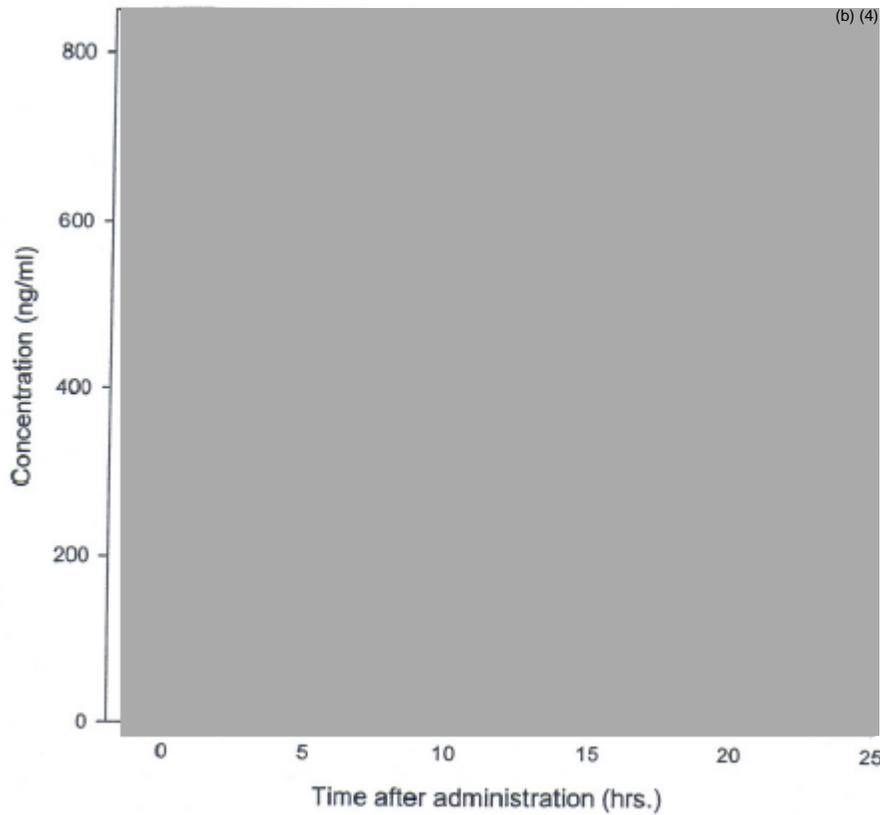
In this study, in Period 1 following an overnight fast, an intravesical dose of 100 mg P-1206 (Hexvix, hexaaminolevulinic acid hydrochloride) containing 11.1 kBq ^{14}C dissolved in 50 mL Solvent for Hexvix was instilled onto the bladder for 1 hour. The evacuated HAL solution was then collected and the remaining C-14-labeled material was analyzed. Blood sampling was performed at baseline and at 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 6, 12, 24, 72, 120, 168, 240, and 336 hours post dosing. The evacuated P-1206 solution was collected and the remaining [^{14}C]-labeled material was analyzed. Following a washout period of 2 weeks, an intravenous dose of 0.15 mg/kg P-1206 3.7 kBq [^{14}C]-P-1206 was infused slowly over a 1-hour period. The blood sampling scheduled and safety follow up was the same as for Period 1.

In plasma, [^{14}C]-labeled material showed a biphasic elimination, with an initial elimination half-life of 39 minutes, followed by a terminal half-life of approximately 76 hours.

For intravesical dose, limit-of-detection (LOD) was similar in all volunteers and an average LOD for all subjects were determined to be 13.52 ng equivalent/ml. The intravenous HAL dose was administered based on the weight of the subject giving a different specific activity for each volunteer. A mean LOD for the intravenous dose was about 4.32 ng equivalent/ml. The plasma concentration after 72 hours sampling were below LOD but for calculation of AUC_{0-336hrs} the measured values between 72-336 hours were used as a best approximation. In addition, the AUC_{0-336 hrs} was calculated using extrapolated values between 72 and 336 hours. For extrapolation, kel was determined between 12-72 hours after the intravenous dose. Kel was then used to extrapolate values for all sampling times for both administrations between 72 and 336 hours. The initial half-life was calculated based on samples within first hour after stop of infusion.

Comparison of AUC_{0-336 hrs} adjusted for difference in dose showed a mean bioavailability of HAL hydrochloride after intra-vesical administration of 7% with a 90% confidence interval of 5-10%.

Figure 1. Individual plasma curves (ng vs hours) following intravesical instillation, 0-24 hrs. Insert: Mean concentration \pm sd for all subjects.



Plasma and whole blood samples were analyzed (b) (4). Samples of drug preparation and Hexvix solution after bladder evacuation, were analyzed (b) (4). For the intravesical dose, LOD was similar in all volunteers and an average (limit-of-detection) LOD for all subjects were determined to be 13.52 ng equivalent/ml. The intravenous HAL dose was administered based on the weight of subject giving a different specific activity for each volunteer. An LOD value for each of the subject giving was therefore calculated for the intravenous dose.

The bioavailability was determined by calculating the AUC using the linear trapezoidal rule and adjusting for the dose administered. The intravesical dose was similar in all subjects, accounting for a small loss of HAL solution in the syringe and catheter used for bladder instillation (Table II). The planned intravesicle dose was 50 ml HAL hydrochloride 100 mg (2mg/ml) and 0.15 mg/kg for the intravenous dose. The intravenous administration was dosed per kg body-weight from a 0.33 mg/ml HAL solution. The percent recovery of C-14 labeled substance after intravesicle administration is shown in Table III. The bioavailability of HAL for each of eight subjects is shown in Table IV.

Table II. Intravesical and intravenous HAL hydrochloride doses

(b) (4)



Table III. Recovery of C-14 labeled substance in the evaluated solution after intravesical instillation.

(b) (4)



Table IV. Bioavailability of HAL hydrochloride after intravesical instillation, by subject

(b) (4)



Table IV. Bioavailability of HAL hydrochloride after intravesical instillation

	Mean	Low 90% CI	High 90% CI
Non-extrapolated data	0.073	0.053	0.102
Extrapolated data	0.093	0.063	0.138

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4.3 Consult Reviews (including Pharmacometric Reviews).....N/A

4.4 Cover Sheet and OCP Filing/Review Form.....N/A

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

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/s/

CHRISTY S JOHN
12/07/2009

YOUNG M CHOI
12/07/2009
I concur.