Department of Urology

**NCT03058705**

# Pilot Study: Assessing Near Infrared Fluorescence Imaging Medical Technology for the Detection of Bladder Cancer

Principal Investigator: Edward Messing, MD, FACS
(Department of Urology)

# 1. PURPOSE OF THE STUDY AND BACKGROUND

## 1.1. Purpose of the study

Primary Aim
The primary outcome of this study is to determine the minimal dwell time needed for adequate detection of Cysview avid tumors using protoporphyrin IX (PpIX) near infrared fluorescence (NIRF).

Secondary Aim
To determine in vivo the ratio of intensity of near infrared fluorescence (NIRF) signal arising from the tumor compared to that arising from normal tissue as a function of dwell time.

## 1.2. Background

Bladder cancer is the fifth most commonly diagnosed solid malignancy in the United States, with patients experiencing multifocal occurrences/recurrences even after seemingly successful treatment of non-muscle invading urothelial cancer. There is level 1 evidence that more complete tumor eradication results in patients experiencing fewer recurrences [1, 2]. Bladder cancer is the most costly malignancy to treat over the lifetime of patients in large part because of the need for multiple re-treatments and surgeries as well as lifelong endoscopic surveillance [3]. Thus, a practical way to improve tumor detection and removal will not only benefit individual patients but also should reduce the overall cost of managing this malignancy.

One method that improves the completeness of transurethral resection of bladder tumors (TURBTs) utilizes intravesical administration of the hematoporphyrin derivative Cysview™ (brand name Hexvix™ elsewhere) to detect tumors not readily visualized with standard white light cystoscopy. Tumor lesions are visualized intra-operatively by shining a blue light throughout the bladder that excites the resultant intracellular PpIX to emit red fluorescence; tumor cells exhibit a lower clearing rate of PpIX because of altered catabolism and transport [4-6], thus it accumulates and permits differential visualization.

Standard of care at UR for diagnosis of bladder tumors consists of white light cystoscopy only in office and then in OR where tumor is biopsied or resected. Fluorescence (blue light cystoscopy) is rarely done in large part because it requires preoperative catheter passage and drug (Cysview) instillation for 60 minutes before surgery (causes patient discomfort) and the actual operation is lengthened. While this technique is efficacious, it requires expensive special equipment, a need to examine the bladder under both white to blue light repeatedly during the case, and the solution (Cysview™) must be instilled 60 minutes before the procedure via a catheter. This inconvenient requirement leads to delay and greater expense for the facility as well as prolonging patient discomfort and apprehension. For these reasons, blue light cystoscopy has not been as widely adopted as one might expect given its clear benefits [1, 2].

We hope to eliminate the obstacles to better care by employing new and more sensitive imaging technologies that should enable more rapid tumor identification and a reduction in bladder dwell time. Agent administration could be done in the operating room just minutes before cystoscopy is performed. We will achieve this by using highly sensitive imaging technologies similar to those used in astronomy to detect near infrared fluorescence (NIRF); this imaging system will detect NIRF emitted by PpIX. Note that conventional blue light cystoscopy detects the red fluorescence emitted by PpIX. This enables two significant advances. First, NIRF can be elicited by white light excitation alone, so there is no need to use separate blue light excitation. Second, the white light image can be simultaneously acquired (viewed and/or recorded) with the NIRF image, so there is no need for switching between the blue light and the white light imaging modes as in conventional blue light cystoscopy.

Thus, this new technology will obviate the need for pre-anesthetic urethral catheterization, the hour wait in the pre-anesthetic area. This reduction in dwell time is made possible by the increased sensitivity of NIRF imaging to PpIX florescence. We have found ex-vivo the NIRF imaging is well over 10 times more sensitive to Cysview florescence than standard blue light cystoscopy. Ex-vivo preliminary studies have shown that blue light cystoscopy can detect PpIX concentrations 1 microgram per milliliter. In contrast, NIRF imaging was able to detect PpIX concentrations down to 0.01 microgram per milliliter, a 100 fold difference (Appendix 4). In addition, as this imaging technology utilizes existing conventional white light cystoscopes, it also averts the requirement for current costly and single purpose blue light generating equipment that cannot be used for other endoscopic procedures.

Many large tumors are readily seen with white light, and we expect to visualize large tumor fluorescence in a few minutes with the new system.

# 2. STUDY DESIGN

## 2.1. **Overview**

The study will be a single center prospective nonrandomized trial of an investigational imaging technology. All patients will undergo investigational imaging and concomitant standard of care transurethral resection of bladder tumor (TURBT). Patients with suspected bladder cancer on cystoscopy will be enrolled to have subsequent intraoperative intravesical administration of Cysview and NIRF cystoscopy immediately prior to TURBT.

## 2.2. **Rationale for Study Design**

Although studies have evaluated optimal dwell time for Cysview fluorescence when cystoscopy is performed under blue light, the optimal dwell time for NIRF visualization has not been determined. Prior to conducting randomized studies comparing efficacy of NIRF and blue light we must first establish that a useful and short dwell time can in fact be used successfully. This pilot study will allow us to identify a dwell time for subsequent NIRF cystoscopy studies.

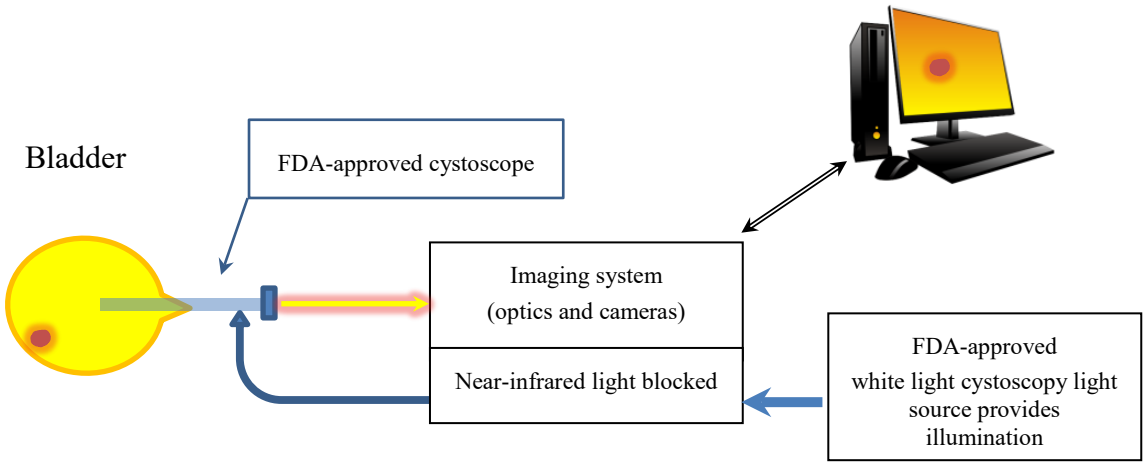
Because from a practical point of view, that is the longest time period we want to prolong surgery with a product that should equal or improve on current blue light cystoscopy. We use blue light very selectively now for these reasons: The Dwell study and the subsequent research that comes from it – should permit avoidance of the pre-op catheterization and significantly shorten the procedure. We have found ex-vivo the NIRF imaging is well over 10 times more sensitive to Cysview florescence and should have no problem with visualization at 10 minutes.

## 2.3. **Rationale for Dosage**

Intravesical instillation of 100 mg Cysview (hexaminolevulinate hydrochloride) will be performed via foley catheter at the initiation of the procedure. Although NIRF is more sensitive than blue light cystoscopy, we will use the current FDA approved dose. Cysview has a favorable safety profile at this dose.

## 2.4. Equipment

This protocol relies on intravesical administration of an FDA-approved agent for bladder cancer detection (Cysview™) that fluoresces upon illumination with an FDA-approved cystoscopic white light source. Standard light sources emit near-infrared wavelengths that would interfere with detecting NIRF, so the cystoscopy light source is filtered to block these wavelengths and thus improve the signal to noise ratio. A standard (FDA-approved) cystoscope is introduced into the bladder and used to guide resection of any detected tumors, i.e. Trans Urethral Resection of Bladder Tumors (TURBT). *Color and near-infrared image streams will be recorded.* The surgeon will be able to display white light images, white light images with pseudocolor highlighting the near-infrared fluorescent tumor, a NIRF image, or a combination of images.



# 3. CHARACTERISTICS OF THE RESEARCH POPULATION

## 3.1. Subject Characteristics

### a) Number of Subjects:

We will enroll 20 subjects to get 10 evaluable subjects in the study. It is expected there may be a high withdrawal rate due to the availability of the study team to all be present on the subject's surgery date.

### b) Gender and Age of Subjects:

Male and female patients who are 18 years or older will be included. Cysview is equally efficacious and safe across both sexes. There is no scientific or medical justification to restrict inclusion of the adult population further by age.

### c) Racial and Ethnic Origin:

There is no restriction of or subject population based on racial or ethnic grounds.

### d) Vulnerable Subjects:

No vulnerable subjects will participate in this study.

## 3.2. Inclusion and Exclusion Criteria

### a) Inclusion Criteria:

- Diagnosis of bladder mass on office cystoscopy suspicious for malignancy, either newly diagnosed or a recurrent tumor
- Planned transurethral resection of bladder tumor in the operating room
- Men or women (age 18 or older)
- Any racial or ethnic origin
- Ability to give informed consent

### b) Exclusion Criteria:

- Pregnancy
- Nursing mother
- Diagnosis of porphyria
- Gross hematuria
- BCG immunotherapy or intravesical chemotherapy within the past 90 days
- Known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid

### 3.3. Discussion of Subject Population

The inclusion/exclusion criteria will be representative of the population that would benefit from reduced Cysview dwell time provided by NIRF cystoscopy. Patients will be excluded based upon the known contraindications for Cysview.

# 4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

### 4.1. Method of Subject Identification and Recruitment

Subjects will be identified through eRecord or clinic schedules by the study team and will be recruited from the clinical offices in the Urology Department at the University of Rochester.

### 4.2. Process of Consent

A member of the study team with routine access to all UR Urology patients will identify potential subjects via eRecord or clinic schedules. Once a potential subject is identified and the urologist notified, the study team will introduce the study at a scheduled clinic visit and check for interest in participation. If interested, eligible subjects may be enrolled at this visit. If potential subjects wish to take the consent form home to read and review with family or friends, a member of the study team will call the patient to check their interest in participation and answer any questions they may have about the study. Informed consent will then be obtained by a member of the study team at their pre-operative visit (see Schedule of Activities – Appendix I).

Subjects will be reminded that they can elect not to participate without risking loss of any present they would normally receive. Any questions the subject may have will be answered. A copy of the signed consent form will be given to the subject and the original consent form will be placed in the research record. All research records will be accessed by the study team and stored in a locked office of the study team. Consent will be obtained in a private setting with a closed door to ensure privacy.

# 5. METHODS AND STUDY PROCEDURES

The study will be a single center prospective nonrandomized trial of an investigational imaging technology. All patients will undergo investigational imaging and the concomitant standard of care, i.e. transurethral resection of bladder tumor (TURBT). Patients with suspected bladder cancer on cystoscopy will be enrolled to have subsequent intraoperative intravesical administration of Cysview and NIRF cystoscopy prior to TURBT.

Ten patients will be recruited to demonstrate the feasibility of using this NIRF imaging system at shorter intravesical instillation durations (Cysview™ dwell time). The instillation duration will be 10, 5, or 2. 5 minutes in this patient series. The subject will be anesthetized, positioned, prepped, and draped for the white light TURBT. A catheter will be passed, Cysview instilled, and the catheter clamped for the assigned dwell time. It will then be unclamped after the dwell time designated, Cysview will be

allowed to drain out, the catheter removed, and cystoscopy performed. The cystoscope is inserted and imaging of the entire bladder commences while recording both color and near-infrared image streams (movies and periodic stills). This initial survey that includes catheterization of the bladder under anesthesia, instillation of Cysview, dwell time as indicated and subsequent evaluation with the color and near-infrared imaging for research purposes. Cysview with blue light cystoscopy has been indicated to be desirable at the time of TURBT but it is not standard of care; it is an optional procedure to increase detection and decrease recurrence. A useful dwell time for Cysview before NIRF imaging will be identified in this study; an effort will be made to minimize the interval between administration and imaging.

The procedure and all study portions will be performed by the subject's surgeon. During the procedure, the bladder will initially be examined in a systematic meridian fashion. Suspicious tumors identified by white light only, NIRF only, and both will be identified. If fluorescence is detected in 3/3 subjects at a given dwell time, the study will continue to shorter dwell times. The initial 3 subjects will have 10 min dwell duration, followed by 5 min and 2.5 min. If fluorescence is not detected in 3/3 subjects at any time period, the study will not progress to shorter dwell times. If no fluorescence is visualized after 10 minutes, we will not proceed to a longer dwell time.

When tumor NIRF is detected, the localized intensity of the fluorescence image will be quantified by comparing the emission arising from the tumor location to the background emission from surrounding normal tissue. The ratio of intensity between the tumor location and the surrounding normal tissue will be used to quantify the signal strength and provide evidence of comparative sensitivity for dwell times.

When the tumor survey is completed, resection of the identified lesions commences according to normal standards of care, i.e. TURBT. Random bladder biopsies are considered standard of care at the time of TURBT. We will take directed biopsies of areas identified by NIRF imaging and treat these as random bladder biopsies.

All specimens will be handled according to standard of care practice and pathologic diagnosis conducted by a genitourinary pathologist.

Study medication will be ordered from the UR Pharmacy and distributed by the Department of Urology at no cost to the subject. Study medication will be stored in a locked cabinet and only accessed by the study team.

Imagin Medical will pay for the cost of the study medication (Cysview) and consigned the NIRF imaging equipment for the study.

5.1. **Treatment Dosage and Administration**

| REGIMEN DESCRIPTION | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-medications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Cysview | None | 100 mg | Bladder instillation by catheter | Intraoperative | 10 minutes maximum |

5.2. **Efficacy Assessments**

This initial series is designed solely to demonstrate that tumors identifiable under white light will be seen to fluoresce in the near-infrared spectrum after relatively short dwell times. We will document detectability of individual tumors under white light and NIRF at short intervals after Cysview instillation.

5.3. **Safety Assessments**

Standard patient preoperative assessment will be performed including medical history, physical exam, vital signs, pertinent clinical labs and pre-anesthesia evaluation if deemed necessary. No additional procedures specific to this study will be performed for safety assessment.

5.4. **Assessment of Subject Compliance**

There are no subject compliance issues to be monitored.

5.5. **Costs to the Subject**

There will be no cost to the subject. The subject will have no additional research visits. Study medication and the use of the NIRF Imaging equipment will be provided by Imagin Medical.

5.6. **Payment for Participation**

There will be no payment for participation.

5.7. **Return of Individual Research Results**

No research results will be provided to the subject. They will have a discussion of resection pathology with their surgeon post procedure as is standard of care.

# 6. CONCOMITANT AND DISALLOWED MEDICATIONS

No medications will preclude participation. No medications will need to be stopped for participation, except as needed for anesthesia and to undergo TURBT (eg. anticoagulants).

# 7. SUBJECT WITHDRAWALS

N/A

# 8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

## 8.1. **Study Drug**

Cysview™ (hexaminolevulinate HCL)

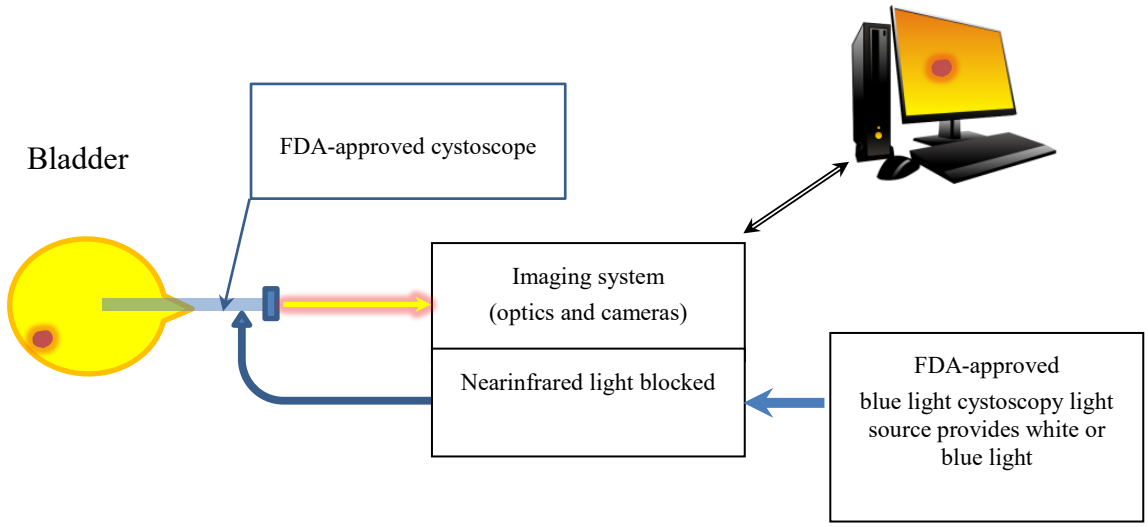
**Study Device**

This protocol relies on intravesical administration of an FDA-approved agent for bladder cancer detection (Cysview™) that will fluoresce upon illumination with an FDA-approved cystoscopic light source. This study will use lowered intensities from the light source; near-infrared wavelengths in the spectral region of interest (spectrally overlapping with NIRF signal) that are emitted by a white light source will be removed with a filter to enable detection of the same wavelengths emitted by tumor fluorescence. The imaging system is new.

A standard (FDA-approved) cystoscope that is currently in use in the SMH OR is introduced into the bladder and is used to guide resection of any detected tumors, i.e. Trans Urethral Resection of Bladder Tumors (TURBT). Color and near-infrared image streams will be recorded. The surgeon will be able to display white light images, white light images with pseudocolor highlighting the near-infrared fluorescent tumor, near-infrared image, or any pair of images. Since the NIRF is in a spectrum that is not visible to the human eye, the computer will display this florescence in a color that is in the visible spectrum or psuedocolor.

Our imaging system does not fit the definition of significant risk device study and therefore qualifies as a non-significant risk device study as follows:

- NIRF imaging is not an implant and does not present a potential for serious risk to health, safety or welfare of a subject.
- NIRF imaging is not for use supporting or sustaining human life.
- Although NIRF imaging will be used during cystoscopy, resection and pathologic diagnosis of cancer will occur independently to NIRF imaging.
- There is no potential for serious risk to health, safety or welfare of the subject




## 8.2. Dosage of Study Drug/Biologic

| REGIMEN DESCRIPTION | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-medications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Cysview | None | 100 mg | Bladder instillation by catheter | Intraoperative | 10 minute maximum |

## 8.3. Subject Enrollment/Randomization

Subjects will be assigned a drug dwell duration based upon the order of study entry. No randomization will occur. The first three study subjects will have a 10 minute dwell time. If the dwell time fluorescence is adequate, dwell time will be reduced to 5 minutes for the next three subjects and then 2.5 minutes accordingly.

## 8.4. Accountability of Investigational Supplies

Study medication will be stored in a locked cabinet and only accessed by the study team. Study medication will be distributed intra-operatively directly by the study team. Any returned medication will be documented within the study subject's research record and disposed of according to the research pharmacy recommendations. The investigational imaging system will be maintained according to operating room standards. The system will be stored in a locked room and only accessed by the study team.

### 8.5. Subject Withdrawal of Study Drug

Subjects who withdraw from the study will not be eligible to re-enroll in the study.

### 8.6. Emergency Drug Disclosure

As this is not a blinded study, emergency drug disclosure does not apply.

## 9. SAFETY AND REPORTABLE EVENTS

### 9.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study intervention.

### 9.2. Serious Adverse Event Definition

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage

### 9.3. Recording Adverse Events

The study staff will assess adverse events by recording all voluntary complaints of the subject post-TURBT (i.e., after Cysview administration in the OR).

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, will be documented on the Adverse Event Summary Log. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, duration, attribution, severity grade, relationship to investigational product (i.e., drug or device), contributing factors, any action taken in response to the study drug/device, and whether the adverse event was expected vs unexpected. The CTCAE (version 4) will be used to assign severity grade of the adverse event.

Adverse events will be documented from the time of Cysview administration until their post-op visit.

### 9.4. **Responsibilities for Reporting Serious Adverse Events**

All serious adverse events will be documented on the Adverse Event Summary Log and subject's research chart. The principal investigator will be notified immediately of any serious adverse events, and subsequently, the RSRB while complying with regulations and RSRB policy regarding the reporting of adverse events. Since Cysview has a favorable safety profile, we do not anticipate any SAE's in this study.

All serious adverse events will be reported to the Wilmot Cancer Institute's Data Safety Monitoring Committee (DSMC) using the DSMC SAE Review Form. All unexpected and related adverse events will be reported to both the RSRB and to the DSMC within 10 calendar days.

## 10. RISK/BENEFIT ASSESSMENT

### 10.1. **Potential Risks**

Known adverse effects of hexaminolevulinate administration include: headache or procedural pain (1%-10%), bladder spasms (2%), bladder pain, dysuria, hematuria (<10%). Abnormal urinalysis, cystitis have been reported (<1%). Anaphylaxis and hypersensitivity reaction has occurred (<1%). [7]

There is no increased risk of adverse effects from the use of the NIRF imaging system. All medications and equipment components in contact with the subject are FDA approved for use in this patient group. Clinical engineering electrical safety certification will be performed. Cystoscopic light sources approved for human use will be used, but at reduced near infrared intensity for imaging purposes; thus less energy is introduced into the patient than would normally occur.

### 10.2. **Protection Against Risks**

To protect subjects from risk, all individuals with hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid will be excluded from participation in this study. The installation time utilized in this study will be 10 minutes as compared with the 60 minute instillation time approved by the FDA, further reducing risk of potential adverse events. Subjects will be hemodynamically monitored by anesthesiologists throughout the instillation which will provide early warning of adverse events if any.

### 10.3. **Potential Benefits to Subjects**

Blue light cystoscopy with the use of Cysview augments identification of hard to visualize tumors and aids in identifying additional areas requiring tumor resection. The use of Cysview with blue light cystoscopy requires dwell times of 60 minutes that is a logistical challenge. The development of highly sensitive detection equipment may allow a reduction of the Cysview dwell time. The reduction in dwell time may also reduce unintended side effects by reducing the duration of mucosal contact with Cysview.

10.4 **Alternatives to Participation**

There are no alternatives to participation. This study is voluntary and subjects do not have to participate.

# 11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

All subjects will be assigned a unique code number and the key will be kept on a password-protected database in a locked office of the study team. Signed consent forms, case report forms, and data collection sheets will be kept in binders in the locked office of the Clinical Trials Office.

Imaging data will be kept on a secure Information Systems Division private network server within the University of Rochester Medical Center. This data will be password-protected, accessible only by study team members listed on this study. The data will be kept indefinitely. Only the study team will have access to the data.

# 12. RESEARCH INFORMATION IN MEDICAL RECORDS

Administration of study medication will be documented in the medical record.

# 13. DATA ANALYSIS AND MONITORING

13.1. **Sample Size Determination**

Conventional blue light cystoscopy has a sensitivity of better than 0.9 (90%) for Ta-T4 tumors. Therefore, the probability that we will fail to detect the tumors in three subjects due to the sensitivity of the blue light method is less than 0.001 (0.1%). We thus believe that 3 subjects represent a sufficient sample size to determine the efficacy of this method.

13.2. **Planned Statistical Analysis**

The procedure will be digitally recorded during simultaneous acquisition of the visible (white light) image and the fluorescence image from separate cameras with precisely aligned fields of view. At any time point, both cameras record the image from the same tissue location as relayed by the cystoscope. Therefore, the images are completely spatially coordinated and the location of any feature (tumor) observed on the white light image will be known in the corresponding image recorded by the fluorescence detection camera. Accordingly, tumors visualized by the white light image should be visible in the fluorescence image as features with enhanced emission. This association thus enables us to determine if PPIX emission arising from tumors is detectable within the specified dwell time. The localized intensity of the fluorescence image will be quantified by comparing the emission arising from the tumor location to the background emission from surrounding normal tissue. The ratio

of intensity between the tumor location and the surrounding normal tissue will be used to quantify the signal strength. We will use this value for further analysis to quantify the signal strength as a function of dwell time.

13.3. **Data and Safety Monitoring**

Study Investigators will conduct continuous review of data and subject safety. The Investigator will submit **semi-annual** progress reports of these data to the Data Safety Monitoring Committee at the Wilmot Cancer Institute for review. The review will include for each treatment arm/dose level: the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed.

The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with the Progress Report to the Data Safety Monitoring Committee at the Wilmot Cancer Institute for review. Actual review dates will be assigned when the first subject is accrued.

- Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the Safety Coordinator at the Wilmot Cancer Institute and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when subject safety is of concern, an interim meeting may be called.

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review at the next quarterly meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The Data Safety Monitoring Committee provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk and complexity of the trial, and is assigned by the Protocol Review Committee at the time of their initial review and approval. The Data and Safety Monitoring Committee will monitor all adverse event rates utilizing a cumulative spreadsheet listing of all events submitted along with progress reports by the PI. All serious adverse events that have occurred in the prior 3 months will be reviewed at the regular quarterly meeting of the DSMC in order to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to current or future subjects.

# 14. REFERENCES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## Appendix 1

Schedule of Activities

| PROCEDURES | Research Visit | Pre-Op Visit | Day of Surgery |
|---|---|---|---|
| Confirm Eligibility | X | X* | |
| Obtain Informed Consent | X | X* | |
| Medical History and Demographics | X | | X^ |
| Concomitant Medication Review | X | | X^ |
| Dispense Study Drug | | | X |
| Near-Infrared Imaging | | | X |
| Adverse Event Review | | | X |

*If not obtained at the Research visit, may be obtained at the Pre-op visit

^If not obtained at the Research visit, may be obtained Day of Surgery

# Appendix 2

## Cysview Packet Insert

# CYSVIEW®
(HEXAMINOLEVULINATE HCL)

PHOTOCURE

### HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Cysview safely and effectively. See full prescribing information for Cysview.**

**Cysview (hexaminolevulinate hydrochloride),** for Intravesical Solution

**For bladder instillation only**

**Initial U.S. Approval: 2010**

### INDICATIONS AND USAGE

Cysview is an optical imaging agent 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).

Important Limitations of Use:

- Not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer. (1.1, 5.2)
- Not for repetitive use. (1.1, 5.1)

### DOSAGE AND ADMINISTRATION

Training in blue light cystoscopy with the Karl Storz D-Light C PDD system is essential prior to the use of Cysview. (2.5)

- Reconstitute Cysview powder with all 50 mL of supplied DILUENT under aseptic conditions. (2.2)
- Use solution of Cysview shortly after reconstitution. If unable to use, the solution may be stored for up to 2 hours in a refrigerator at 2°-8°C (36°-46°F) in labeled syringe. Discard after 2 hours. (2.2, 16)
- Instill 50 mL of reconstituted solution of Cysview into the emptied bladder via an intravesical catheter. Retain in the bladder for 1 hour before evacuating and performing cystoscopic examination. (2.3, 2.5)
- First perform a complete cystoscopic examination of the entire bladder under white light and then repeat the examination of the entire bladder under blue light. Record and document information about location and appearance of suspicious lesions and areas seen under both white and blue light. (2.5)

### DOSAGE FORMS AND STRENGTHS

Cysview (hexaminolevulinate hydrochloride) is supplied as a kit containing:

- A 10 mL glass vial containing 100 mg powder of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution.
- A polypropylene vial containing 50 mL DILUENT for Cysview.
- One Luer Lock catheter adapter. (16)

Once reconstituted, the solution contains 2 mg/mL (6 mmol/L) of hexaminolevulinate hydrochloride.

### CONTRAINDICATIONS

Do not use Cysview in patients with:

- porphyria,
- gross hematuria,
- BCG immunotherapy or intravesical chemotherapy within the past 90 days, or
- known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives. (4)

### WARNINGS AND PRECAUTIONS

- Anaphylaxis: have trained personnel and therapies available. (5.1)
- Failed Detection: Cysview may not detect all malignant lesions. Always perform white light cystoscopy (Mode 1) followed by blue light cystoscopy (Mode 2). Do not biopsy with blue light only. (5.2)
- False fluorescence may occur due to inflammation, cystoscopic trauma, scar tissue or previous bladder biopsy. (5.3)

### ADVERSE REACTIONS

The most common adverse reaction reported in patients who received Cysview was bladder spasm, occurring in < 3% of patients, followed by dysuria, hematuria, bladder pain, procedural pain, urinary retention and headache, all occurring in ≤ 2% of patients. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Photocure Inc. at 1-855-297-8439 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### USE IN SPECIFIC POPULATIONS

- Pregnancy Category C: No human or animal data. Use only if clearly needed. (8.1)
- Nursing mothers: No human or animal data. Exercise caution when Cysview is administered to nursing mothers. (8.3)
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 11/2011**

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### FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed.

### FULL PRESCRIBING INFORMATION

#### 1 INDICATIONS AND USAGE

Cysview is an optical imaging agent 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).

#### 1.1 Limitations of Use

Cysview is not:

- a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer [*see Warnings and Precautions (5.2)*].
- for repetitive use. The potential risks associated with repetitive exposure, including sensitization and adverse effects of blue light, have not been evaluated [*see Warnings and Precautions (5.1)*].

#### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

The recommended dose for adults is 50 mL of reconstituted solution of Cysview [*see Dosage and Administration (2.2)*] instilled into the bladder via a urinary catheter [*see Dosage and Administration (2.3)*].

#### 2.2 Reconstitution of Cysview

Cysview is supplied as a kit containing two vials: a clear glass vial labeled as Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, containing 100 mg hexaminolevulinate hydrochloride as a powder, and a vial labeled as DILUENT for Cysview, containing 50 mL of the diluent in a polypropylene vial.

Perform all steps under aseptic conditions. Use gloves during the reconstitution procedure; skin exposure to hexaminolevulinate hydrochloride may increase the risk for sensitization to the drug.

Use a 50 mL syringe with a Luer Lock tip throughout the reconstitution procedure to ensure that the correct concentration (2 mg/mL) of the drug is obtained and that a stable syringe-catheter connection is made for the bladder instillation of Cysview.

**Figure 1.**

1. Remove the cap from the sterile 50 mL syringe and carefully retain it for subsequent reattachment to the syringe (step 4). Attach a needle to the syringe and withdraw 50 mL of the diluent (Figure 1).

**Figure 2.**

2. Penetrate the stopper of the Cysview powder vial with the needle and inject 10 mL of the diluent from the syringe into the powder vial (Figure 2).

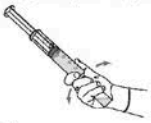


**Figure 3.**

3. Without withdrawing the needle from the vial, hold the powder vial and syringe in a firm grip (Figure 3) and gently shake to dissolve of the powder in the diluent. The powder normally dissolves almost immediately.

**Figure 4.**

4. Withdraw all of the dissolved solution from the powder vial (10 mL) into the 50 mL syringe (Figure 4).

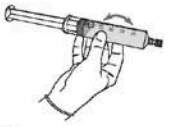


**Figure 5.**

5. Remove the needle from the powder vial, disconnect the needle from the syringe tip and discard it. Plug the syringe with the syringe cap (Figure 5). Gently mix the contents of the syringe. The reconstituted solution of Cysview is colorless to pale yellow and clear to slightly opalescent, and free from visible particles.

**Figure 6.**

6. Peel off the detachable portion of the label (starting at the corner marked with a black triangle) from the Cysview powder vial and affix it to the syringe containing the solution of Cysview (Figure 6). Add two hours to the present time and write the resulting expiration time and date on the syringe label.

Cysview is now reconstituted and ready for use. Instill the reconstituted solution of Cysview into the bladder. If unable to administer the solution shortly after reconstitution, the solution may be stored for up to 2 hours in a refrigerator at 2°-8°C (36°- 46°F) in the labeled syringe. If not used within 2 hours, discard the solution. [*see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)*]

#### 2.3 Bladder Instillation of Cysview

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 adapter. Use only catheters made of vinyl (uncoated or coated with hydrogel), latex (amber or 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.

Use the following steps for bladder instillation of Cysview.

1. Using standard sterile catheterization technique, first insert the urethral catheter into the bladder of the patient and use the catheter to completely empty the patient's bladder before instillation of Cysview.

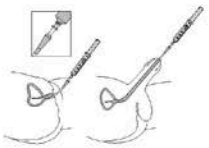


**Figure 7.**

2. To attach the syringe containing the solution of Cysview to the catheter, do the following:

- Remove the syringe cap from the 50 mL syringe that contains the solution of Cysview.
- Attach the Luer Lock end of the (provided) catheter adapter to the syringe.
- Insert the tapered end of the catheter adapter into the funnel opening of the catheter. See Figure 7, with the connection enlarged in the inset.

3. Slowly instill the solution of Cysview into the bladder through the catheter (Figure 7), ensuring that the complete volume of the syringe (50 mL) is administered.

4. After the solution is instilled, remove the catheter and instruct the patient to retain the solution within the bladder for at least 1 hour; do not exceed 3 hours [*see Dosage and Administration (2.4)*]. Patients may stand, sit and move about during the time period between instillation and start of the cystoscopic procedure.

5. Evacuate the solution of Cysview from the bladder as part of routine emptying of the bladder immediately prior to the initiation of the cystoscopic procedure (refer to the Karl Storz PDD Telescope Instruction manual). Also, the patient may void and completely empty the bladder prior to the procedure.

Avoid skin contact with Cysview. If skin does come in contact with Cysview, wash immediately with soap and water and dry off. After voiding the bladder of Cysview, routinely wash the patient's perineal skin region with soap and water and dry.

#### 2.4 Use of the Karl *Storz* D-Light C Photodynamic Diagnostic (PDD) System

Cysview imaging requires the use of the Karl Storz D-Light C PDD system, which consists of a light source, a camera and a telescope. The light source enables both white light cystoscopy and blue light (wavelength 360 – 450 nm) fluorescence cystoscopy. Familiarity with this system is essential before beginning the procedure and before instilling Cysview into the bladder. For system set up and general information for the safe use of the PDD system, refer to the Karl Storz instruction manual for the PDD system and the instruction manuals for each of the system components. The PDD System is not for use by healthcare providers with green-red color blindness.

#### 2.5 Cystoscopic Examination

*Training*

Training and proficiency in cystoscopic procedures are essential prior to the use of Cysview. Carefully review the instruction manuals provided with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) System. For additional training in the use of the PDD System, contact the manufacturer's representative.

*Preparation for Cystoscopy*

Initiate the cystoscopic examination within 30 minutes after evacuation of Cysview from the bladder, but no less than 1 or more than 3 hours after Cysview is instilled in the bladder. If the patient did not retain Cysview in the bladder for 1 hour, allow 1 hour to pass from the instillation of Cysview into the bladder to the start of the cystoscopic examination. The efficacy of Cysview has not been established when the solution was retained for less than 1 hour.

*Cystoscopic Examination*

Empty the patient's bladder and then fill the bladder with a clear fluid (standard bladder irrigation fluid) in order to distend the bladder wall for cystoscopic visibility. Ensure adequate irrigation during examination of the bladder; blood, urine or floating particles in the bladder may interfere with visualization under both white light and blue light.

First perform a complete cystoscopic examination of the entire bladder under white light (Mode 1) and then repeat the examination of the entire bladder surface under blue light (Mode 2) unless the white light cystoscopy reveals extensive mucosal inflammation. Do not perform the blue light cystoscopy if the white light cystoscopy reveals wide-spread mucosal inflammation. Abnormalities of the bladder mucosa during blue light cystoscopy are characterized by the detection of red, homogenous and intense fluorescence. The margins of the abnormal lesions are typically well-demarcated and in contrast to the normal urothelium, which appears blue. Register and document (map) the location and appearance (e.g. papillary) of suspicious lesions and abnormalities seen under either white or blue light.

During the cystoscopic examination, be aware that:

- a red fluorescence is expected at the bladder outlet and the prostatic urethra; this fluorescence occurs in normal tissue and is usually less intense and more diffuse than the bladder mucosal fluorescence associated with malignant lesions.
- tangential light may give false fluorescence.

To help avoid false fluorescence, hold the endoscope perpendicular and close to the bladder wall with the bladder distended.

- false positive fluorescence may result from scope trauma from a previous cystoscopic examination and/or bladder inflammation *[see Warnings and Precautions (5.3)]*.
- malignant lesions may not fluoresce following Cysview administration, particularly if the lesions are coated with necrotic tissue. Blue light may fail to detect Ta tumors which have a tendency to be necrotic on the surface, and necrotic cells generally do not fluoresce *[see Warnings and Precautions (5.3)]*.
- when performing the blue light cystoscopy, avoid prolonged blue light exposure. Studies have not evaluated the potential for adverse effects from blue light. In the controlled clinical trial, the cumulative blue light exposure from bladder mapping did not exceed 12 minutes and checking for complete tumor resection under blue light did not exceed 8 minutes for any patient *[see Clinical Studies (14)]*.

Perform biopsy and/or resection of suspicious lesions by transurethral resection of the bladder (TURB) only after completing white and blue light cystoscopic examinations with bladder mapping. Using standard cystoscopic practices, obtain biopsies of abnormal areas identified during either white or blue light examination and perform resections. Always check for the completeness of the resections under both white light and blue light before finalizing the TURB procedure.

## 3 DOSAGE FORMS AND STRENGTHS

Cysview (hexaminolevulinate hydrochloride) is supplied as a kit containing:

- Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg, as a powder in a 10 mL clear glass vial.
- DILUENT for Cysview, 50 mL, in a polypropylene vial.
- One Luer Lock catheter adapter (to connect the syringe containing the reconstituted solution of Cysview to the urethral catheter for bladder instillation of Cysview).

Once reconstituted, the solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride.

## 4 CONTRAINDICATIONS

Cysview is contraindicated in patients with:

- porphyria
- gross hematuria
- BCG immunotherapy or intravesical chemotherapy within the past 90 days
- known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Anaphylaxis

Anaphylaxis, including anaphylactoid shock, has been reported following administration of Cysview *[see Adverse Reactions (6.2)]*. Prior to and during use of the Cysview, have trained personnel and therapies available for the treatment of anaphylaxis. The safety of repetitive Cysview exposures has not been evaluated.

### 5.2 Failed Detection

Cysview may fail to detect some bladder tumors, including malignant lesions. Cysview is not a replacement for random biopsies or any other procedure usually performed in the cystoscopic evaluation for cancer. In the controlled clinical trial, Cysview failed to detect 10% of lesions confirmed as malignant within the study drug group *[see Clinical Studies (14)]*. Do not perform cystoscopy with blue light alone as malignant lesions can be missed unless the bladder is initially examined under white light *[see Dosage and Administration (2.5)]*.

### 5.3 False Fluorescence

Fluorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. In the controlled clinical study, biopsies from one of every four fluorescent areas showed neither dysplasia nor carcinoma. If the areas were not also identified during white light cystoscopy *[see Clinical Studies (14)]*. In addition to these false detections, fluorescent areas within the bladder mucosa may result from inflammation, cystoscopic trauma, scar tissue or bladder mucosal biopsy from a previous cystoscopic examination.

The presence of urine and/or blood within the bladder may interfere with the detection of tissue fluorescence. To enhance the diagnostic utility of Cysview with the Karl Storz D-Light C PDD System:

- ensure the bladder is emptied of urine prior to the instillation of fluids at cystoscopy.
- biopsy/resect bladder mucosal lesions only following completion of both white light and blue light cystoscopy.

## 6 ADVERSE REACTIONS

Anaphylaxis has been reported following exposure to Cysview *[see Warnings and Precautions (5.1)]*.

### 6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In six clinical trials, safety data were obtained from 1,324 patients, aged 32 to 96 years with a median age of 69 years, all primarily Caucasian and approximately 76% male. All patients were evaluated after a single instillation of 50 mL solution of Cysview. Of these patients, 161 (12.2%) patients reported at least one adverse reaction. The most common adverse reaction was bladder spasm (reported in 2.2% of the patients) followed by dysuria, hematuria, and bladder pain. No patients experienced anaphylaxis. In the controlled clinical study, adverse reactions were similar in nature and rate between the study drug group and the control group *[see Clinical Studies (14)]*.

### 6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis and abnormal urinalysis have been reported during post marketing use of Cysview.

## 7 DRUG INTERACTIONS

No specific drug interaction studies have been performed.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Adequate reproductive and developmental toxicity studies in animals have not been performed. Cysview should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.3 Nursing Mothers

It is not known whether hexaminolevulinate is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when Cysview is administered to nursing mothers.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

Of 1823 subjects in clinical studies of Cysview, 67% were 65 years and over while 34% were 75 years and over. No clinically important differences in safety or efficacy have been observed between older and younger patients in the controlled study.

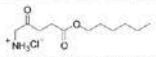
## 10 OVERDOSAGE

No adverse events were reported in a dose-finding study conducted among patients whose bladders were instilled with twice the recommended concentration (dose) of solution of Cysview.

## 11 DESCRIPTION

Cysview contains hexaminolevulinate hydrochloride, an optical imaging drug that in solution form is instilled intravesically for use with photodynamic blue light cystoscopy as an adjund to white light cystoscopy.

The chemical formula for hexaminolevulinate hydrochloride is $C_6H_{13}NO_3HCl$. Its molecular weight is 251.76 and it has the following structural formula:



Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution is intended for intravesical administration only after reconstitution with the supplied 50 mL DILUENT. Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution and DILUENT for Cysview are supplied together as a kit.

Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution is supplied as a sterile, non-pyrogenic, freeze-dried, white to off-white or pale yellow powder containing 100 mg of hexaminolevulinate hydrochloride (equivalent of 85 mg of hexaminolevulinate) in a 10 mL clear glass vials. The DILUENT for Cysview is a sterile, non-pyrogenic solution (pH 6) containing 0.61 mg/mL disodium hydrogen phosphate, 0.58 mg/mL of potassium dihydrogen phosphate, 7.02 mg/mL of sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection. It is a clear, colorless solution, free from visible particles, and is provided in a 50 mL polypropylene vial.

The reconstituted solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride and is colorless to pale yellow. It is free from visible particles and has a pH between 6.7 and 8.2.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Cysview is an ester of the heme precursor, aminolevulinic acid. After bladder instillation, Cysview enters the bladder mucosa and is proposed to enter the intracellular space of mucosal cells where it is used as a precursor in the formation of the photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs). PpIX and PAPs are reported to accumulate preferentially in neoplastic cells as compared to normal urothelium, partly due to altered enzymatic activity in the neoplastic cells. After excitation with light at wavelengths between 360 and 450 nm, PpIX and other PAPs return to a lower energy level by fluorescing, which can be detected and used for cystoscopic detection of lesions. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Similar processes may occur in inflamed cells.

### 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 360 – 450 nm, the porphyrins will fluoresce red *[see Dosage and Administration (2.5)]*.

### 12.3 Pharmacokinetics

After bladder instillation of [$^{14}$C]-labeled Cysview (100 mg) for approximately 1 hour in healthy volunteers, absolute bioavailability of Cysview was 7% (90% confidence interval (CI): 5%-10%). The [$^{14}$C]-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 analyses showed no evidence of significant binding of Cysview to erythrocytes. An *in vitro* study showed that Cysview underwent rapid metabolism in human blood.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies in animals have been conducted to evaluate the carcinogenic potential of hexaminolevulinate hydrochloride.

Hexaminolevulinate hydrochloride was not mutagenic in *in vitro* reverse mutation tests in bacteria, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of doses up to 45 mg/kg in the absence of light activation. Adequate studies have not been performed to evaluate the genetic toxicity of hexaminolevulinate hydrochloride in the presence of light activation.

Adequate reproductive and developmental toxicity studies in animals have not been performed to evaluate the effects of hexaminolevulinate hydrochloride on fertility.

### 13.2 Animal Toxicology and/or Pharmacology

Dose dependent neurological effects such as tremor, increased motor activity, and increased startle and touch escape responses were observed immediately after dosing at doses ≥ 30 mg/kg (24 times human systemic exposure based on the body surface area, using 10% as the upper level of 90% confidence interval of bioavailability) in a single dose rat study. The animals recovered to normal status by 60 min after dosing. Adverse neurological effects were also noted in other single or repeat dose toxicity studies.

Hexaminolevulinate hydrochloride had moderate to strong potential to cause skin sensitization based on a local lymph node assay in mouse.

## 14 CLINICAL STUDIES

The safety and efficacy of Cysview when used with photodynamic cystoscopy were studied in a prospective, multicenter, controlled clinical trial. Adult patients with known or suspected bladder cancer were randomized to either white light (WL) cystoscopy (control group, n = 384) or WL followed by blue light (BL) cystoscopy (study drug group, n = 388). Only the study drug group patients received Cysview by bladder instillation prior to cystoscopy. After bladder evacuation of Cysview, bladder lesion mapping was performed initially using the Karl Storz PDD system in the WL mode followed by lesion mapping in the BL mode. Control group patients underwent only WL cystoscopy with lesion mapping. The average age of the randomized patients was 69 years (range 24 to 96); 78% were male and 94% were Caucasian. All patients had previously undergone cystoscopy.

The main diagnostic efficacy outcome was assessed within the study drug group. This assessment compared lesions detected during an initial cystoscopic examination to their centralized histologic findings (the standard of truth). Following the initial diagnostic cystoscopy, patients within both study groups who had histologically confirmed Ta and/or T1 lesions underwent follow-up WL cystoscopy at 3, 6 and 9 months; these histologic evaluations were based upon the site assessments at both the initial and follow-up cystoscopy.

Diagnostic efficacy assessed the number of patients within the study drug group who had at least one additional Ta or T1 bladder cancer detected only by BL; the proportion of these patients was compared to a proposed threshold proportion of 10%. Within the study drug group, 286 patients had at least one Ta and/or T1 lesion, including 47 patients who had at least one of the lesions detected only by BL (see Table 1).

**Table 1: BL Cystoscopic Ta and/or T1 Lesion Detection within the Study Drug Group**

| | |
|---|---|
| Number of patients with any Ta and/or T1 lesion detected with either WL or BL | 286 |
| Number (%) of patients with any Ta and/or T1 lesion detected only with BL | 47 (16%) |
| p-value* | 0.001 |

*exact test comparison of the proportion to a threshold value of 10%

Some malignant lesions were detected only by WL or BL (see Table 2).

**Table 2: Bladder Tumor Detection within the Study Drug Group by WL and/or BL Cystoscopy**

| Number of lesions | Detected by Both WL & BL | Detected by WL Only | Detected by BL Only |
|---|---|---|---|
| CIS, n = 65 | 33 | 5 | 27 |
| Ta, n = 580 | 472 | 52 | 56 |
| T1, n = 95 | 76 | 10 | 9 |
| T2 – T4, n = 47 | 38 | 8 | 1 |

Among the lesions detected only by BL, 23% were negative for any carcinoma-related pathology, including dysplasia. Among the lesions detected only by WL, 17% were negative for any carcinoma-related pathology, including dysplasia.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Cysview is supplied as a kit labeled Cysview (hexaminolevulinate hydrochloride) Kit for Intravesical Solution, 100 mg. The kit contains:

- One vial of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg, as a powder in a 10 mL clear glass vial.
- One vial of DILUENT for Cysview, 50 mL, in a polypropylene vial.
- One Luer Lock catheter adapter (to connect the syringe containing Cysview solution to the urethral catheter during instillation of Cysview).

NDC 10511-3001-1

### Storage

Store Cysview (hexaminolevulinate hydrochloride) Kit for Intravesical Solution at 20°-25°C (68°-77°F); excursions are permitted to 15°-30°C (59°-86°F). Do not use beyond the expiry date printed on the carton.

Use the solution of Cysview shortly after reconstitution. If unable to use within this time period, the reconstituted solution can be stored under refrigeration at 2°-8°C (36°-46°F) for up to 2 hours in the 50 mL labeled syringe.

## 17 PATIENT COUNSELING INFORMATION

Ask patients if they have:

- a diagnosis or a family history of porphyria
- allergy to aminolevulinic acid or prior exposure to Cysview
- gross hematuria
- had BCG immunotherapy or chemotherapy within the bladder.

Inform patients that Cysview should be retained in the bladder for 1 hour from instillation of Cysview to the start of the cystoscopic procedure. If the patient cannot hold Cysview for 1 hour, but needs to void and expel Cysview from the bladder, he or she may void and should then inform a health care professional *[see Dosage and Administration (2)]*.

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## Appendix 3

Data Collection Form

| Subject Number | Male or Female | Age | History of Bladder Cancer | Video File | Dwell Time | Adequate Assessment of Florescence | Pathology of Directed Biopsies | Pathology of Primary Specimen |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

## Appendix 4

Preliminary ex-vivo results: Comparison of sensitivity between imaging modalities