PRODUCT MONOGRAPH

PrCYSVIEW®

Hexaminolevulinate hydrochloride for intravesical solution
100 mg/vial

Kit for the preparation of intravesical solution

Other diagnostic agents

Photocure ASA
Hoffsveien 4
0275 Oslo
Norway

Imported by:
Innomar Strategies Inc.
3470 Superior Court,
Oakville, ON L6L 0C4

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
Intravesical	Cysview 100 mg kit for the preparation of 1.7 mg/mL hexaminolevulinate solution.	None [for a complete listing see DOSAGE FORMS, COMPOSITION, AND PACKAGING]

INDICATIONS AND CLINICAL USE

Cysview (hexaminolevulinate hydrochloride) is indicated as:

An adjunct to white-light cystoscopy in the detection of non-muscle invasive papillary bladder cancer in patients with known or suspected bladder cancer.

Only approved cystoscopic equipment should be used, equipped with necessary filters to allow both white-light cystoscopy (WLC) and blue-light (wavelength 360–450nm) fluorescence cystoscopy (BLC). Training in blue-light cystoscopy with an approved Photodynamic Diagnosis (PDD) System is essential prior to the use of Cysview.

CONTRAINDICATIONS

- Cysview is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section;
- Cysview is contraindicated in patients with porphyria.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Very rare cases of hypersensitivity, including anaphylactic shock, have been reported during post-marketing use of Cysview [see ADVERSE REACTIONS].
Advanced life support facilities should be readily available.

Genitourinary

Do not use in patients with gross hematuria.

Cysview should not be used in patients at high risk of bladder inflammation, e.g. less than 90 days after intravesical Bacillus Calmette–Guérin (BCG) or chemotherapy, as inflammation caused by these treatments may lead to false fluorescence.

Cysview should not be used for retrograde uretero-renoscopy. Administration into the ureters can result in anuria.

Immune

Anaphylactoid/hypersensitivity reactions characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock have occurred after Cysview administration [see ADVERSE REACTIONS]. It is important to be familiar with the practice of emergency measures so that prompt action may be taken in the event of hypersensitivity reactions. To permit immediate countermeasures to be taken in emergencies, appropriate drugs and instruments (e.g., endotracheal tube and ventilator) should be readily available.

The potential for Cysview to cause delayed hypersensitivity reactions occurring hours or days after administration cannot be excluded. Therefore, post-procedure observation of the patient is recommended for at least 30 minutes after the administration of Cysview.

Skin

Cysview may cause sensitisation upon contact with the skin.

Carcinogenesis and Mutagenesis

Please see TOXICOLOGY section. All the studies of genotoxic potential were negative. No long term studies to evaluate the carcinogenicity potential of Cysview have been performed.

Special Populations

Pregnant Women: There is no experience in the use of Cysview in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryofetal toxicity, teratologic effects or female fertility [see TOXICOLOGY]. Cysview should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: It is unknown whether Cysview or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Cysview.

Geriatrics (≥ *65* years of age):

Evidence from clinical studies suggests that there are no overall differences in safety and efficacy between patients aged 65 years and older or younger patients.

Pediatrics:

Safety and Efficacy have not been studied in pediatric populations.

Failed Detection

Cysview may fail to detect some bladder tumours, 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 trials, Cysview failed to detect up to 10% of lesions confirmed as malignant within the study drug group. Do not perform cystoscopy with blue light alone as malignant lesions can be missed unless the bladder is initially examined under white light.

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. 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 an approved PDD System:

- Ensure the bladder is emptied of urine prior to the instillation of fluids at cystoscopy;
- The bladder should be sufficiently distended to ensure that the whole bladder can be inspected;
- Biopsy/resect bladder mucosal lesions only following completion of both white-light and blue-light cystoscopy.

Photobleaching:

Photobleaching may be noticed during extensive use of fluorescence-guided resection. However, regeneration of fluorescence may be seen in areas kept 'in the dark' for a few minutes. To minimise photobleaching, the use of white light should be performed under the lowest possible light intensity.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypersensitivity, including anaphylactoid shock (4 cases in >210 000 exposures), has been reported post-marketing following exposure to Cysview.

Most of the reported adverse reactions after Cysview were transient and mild or moderate in intensity, occurring in the genitourinary system, and were similar in nature and severity to those observed after white-light cystoscopy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reactions observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In six clinical trials with Cysview, safety data were obtained from 1,324 patients. Table 1 lists adverse drug reactions that occurred in ≥1% of patients in controlled clinical studies with Cysview. Most of the reported adverse reactions were transient and mild or moderate in intensity.

Table 1: Summary of Adverse Reactions Occurring in ≥ 1% of Patients by Body System, Preferred Term and Severity in the Controlled Studies

MedDRA Body System Preferred Term	Cysview N = 1,324			
	Mild n (%)	Moderate n (%)	Severe n (%)	Sum n (%)
Number of adverse reactions with unique preferred terms	141	128	19	288
Injury, poisoning, and procedural complications	**6 (0.5%)**	**16 (1.2%)**	**0 (0.0%)**	**22 (1.7%)**
Procedural pain	4 (0.3%)	14 (1.1%)	0 (0.0%)	18 (1.4%)
Nervous system disorders	**8 (0.6%)**	**8 (0.6%)**	**0 (0.0%)**	**16 (1.2%)**
Headache	8 (0.6%)	6 (0.5%)	0 (0.0%)	14 (1.1%)
Renal and urinary system disorders	**48 (3.6%)**	**45 (3.4%)**	**11 (0.8%)**	**104 (7.9%)**
Bladder spasm	19 (1.4%)	9 (0.7%)	4 (0.3%)	32 (2.4%)
Dysuria	12 (0.9%)	12 (0.9%)	0 (0.0%)	24 (1.8%)
Bladder pain	5 (0.4%)	15 (1.1%)	3 (0.2%)	23 (1.7%)
Hematuria	15 (1.1%)	7 (0.5%)	1 (0.1%)	23 (1.7%)
Urinary retention	5 (0.4%)	10 (0.8%)	2 (0.2%)	17 (1.3%)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and lymphatic system disorders: anemia, leukocytosis.
Cardiac disorders: arrhythmia, tachycardia.
Congenital, familial and genetic disorders: phimosis.
Gastrointestinal disorders: abdominal pain, abdominal pain upper, constipation, diarrhea, nausea, vomiting.
General disorders and administration site conditions: asthenia, chest pain, chills, fatigue, influenza like illness, peripheral coldness, pyrexia.
Infections and infestations: cystitis, sepsis, urinary tract infection, vaginal infection.
Injury, poisoning, and procedural complications: postoperative fever, post-procedural haemorrhage, urinary retention postoperative.
Investigations: blood bilirubin increased, blood urine present, hepatic enzyme increased, white blood cell count increased.
Metabolism and nutrition disorders: gout.
Musculoskeletal and connective tissue disorders: back pain, flank pain, muscle spasm.
Neoplasms benign, malignant, and unspecified (including cysts and polyps): bladder cancer recurrent.
Nervous system disorders: dizziness, dizziness postural, migraine.
Psychiatric disorders: depression, disorientation, insomnia.
Renal and urinary system disorders: bladder distension, calculus bladder, contracted bladder, incontinence, micturition urgency, nocturia, pollakiuria, urethral pain, urinary bladder hemorrhage, urinary tract disorder.
Reproductive system and breast disorders: balanitis, penile pain, penile swelling.
Respiratory, thoracic and mediastinal disorders: lung disorder, rales.
Skin and subcutaneous tissue disorders: rash, pruritus, urticaria.
Vascular disorders: flushing, haemorrhage, hypertension, hypotension.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials conducted with Cysview, no trends were observed for hematology parameters.

Post-Market Adverse Drug Reactions

Very rare cases of hypersensitivity, including anaphylactic shock, have been reported during post-marketing use of Cysview.

The following drug-related adverse events were reported spontaneously post marketing:

Table 2: Spontaneous post marketing reports of drug-related adverse events

System Organ Class (MedDRA)	Frequency	Adverse reaction
Cardiac Disorders	Very rare	Atrial fibrillation, Bradycardia, Coronary artery stenosis, Tachycardia
Eye disorders	Very rare	Eye irritation, Photophobia
Gastrointestinal disorders	Very rare	Abdominal pain, Nausea, Vomiting
General disorders and administration site conditions	Very rare	Chest discomfort, Chills, Drug ineffective, Feeling hot, Pain, Pyrexia
Immune system disorders	Very rare	Anaphylactoid shock, Hypersensitivity
Infections and infestations	Very rare	Cystitis, Sepsis, Urosepsis
Injury, poisoning and procedural complications	Very rare	Accidental exposure, Thermal burn
Investigations	Very rare	Blood creatinine increased, Blood pressure decreased, C-reactive protein increased, ECG signs of myocardial ischemia, Haemoglobin decreased, Heart rate decreased, Red blood cell count increased, Troponin T increased, Vital functions abnormal, White blood cell count increased
Nervous system disorders	Very rare	Dizziness postural, Loss of consciousness, Paraesthesia
Renal and urinary disorders	Very rare	Anuria, Bladder irritation, Haematuria, Haemorrhage urinary tract, Micturition urgency, Renal pain, Urinary retention
Respiratory, thoracic and mediastinal disorders	Very rare	Dyspnoea, Pharyngeal oedema, Pulmonary oedema
Skin and subcutaneous tissue disorders	Very rare	Cold sweat, Cutaneous vasculitis, Erythema, Pruritus, Rash generalised, Skin lesions, Skin necrosis, Vascular purpura
Vascular disorders	Very rare	Flushing, Hypotension

The adverse reactions are classified by System Organ Class and frequency using the following convention: Very common (>1/10), Common (>1/100 to < 1/10), Uncommon (> 1/1,000 to < 1/100), Rare (> 1/10,000 to < 1/1,000), Very rare (< 1/10,000) including isolated reports.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with Cysview.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory test results have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

No dosing adjustments are required.

Recommended Dose and Dosage Adjustment

50 mL of the 8 mmol/L Cysview solution [see Reconstitution] is instilled into the bladder through a catheter. 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.

Repeated dose

The potential risks associated with repetitive exposure, including sensitization and adverse effects of blue light have not been evaluated in the clinical trials.

Missed Dose

Not applicable.

Administration

Reconstitution:

Handling instructions for the pharmacist or other healthcare professionals:

All steps should be performed with sterile equipment and under aseptic conditions. Wear gloves during the reconstitution procedure; skin exposure to hexaminolevulinate hydrochloride may increase the risk for sensitization to the drug.

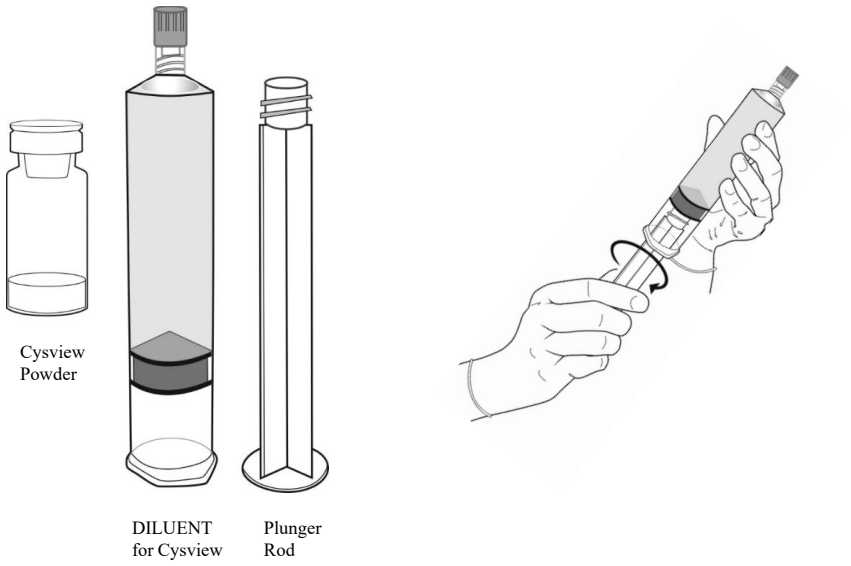


Figure 1

1. Fasten the plunger rod into the rubber stopper of the pre-filled syringe by turning the plunger rod clockwise until it stops (Figure 1).

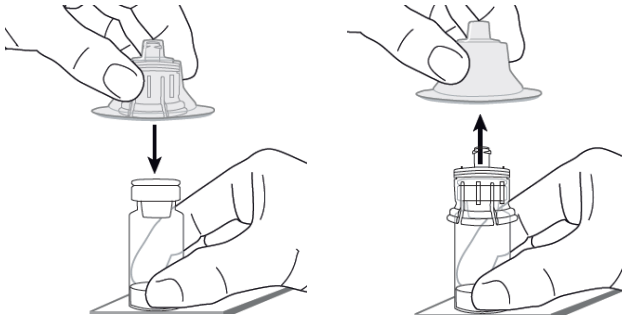


Figure 2

2. Remove the plastic cap from the vial. Remove the TyveK® cover from the vial adapter blister package. Do not remove the vial adapter from the package. Place the Cysview powder vial on a flat surface.

   Using the blister package to hold the vial adapter, connect to the vial with a downward vertical motion. The vial adapter snaps onto the vial as the spike penetrates the rubber stopper of the vial.

   Remove the plastic blister package and discard it. Take care not to touch the exposed end of the vial adapter (Figure 2).

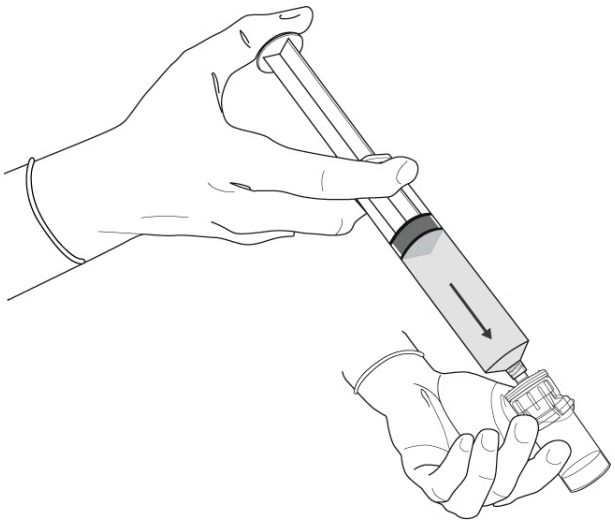


Figure 3

3. Remove the cap from the pre-filled syringe and carefully retain it for subsequent reattachment to the syringe (step 6).

   Hold the pre-filled syringe upright and carefully press the plunger rod upward to remove air. Connect the syringe to the vial adapter.

   Inject about 10 mL of the DILUENT from the pre-filled syringe down into the powder vial. The vial should be about ¾ full (Figure 3).

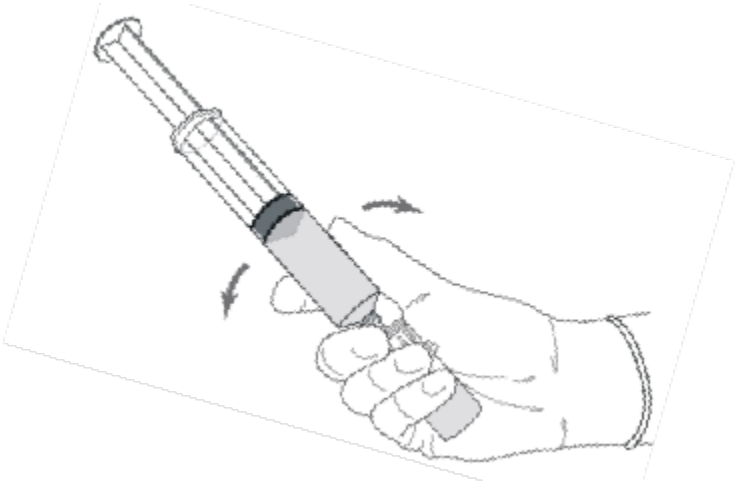


Figure 4

4. Without disconnecting the vial adapter from the vial, hold the powder vial and syringe in a firm grip (Figure 4) and gently shake to dissolve the powder in the DILUENT. The powder normally dissolves almost immediately.

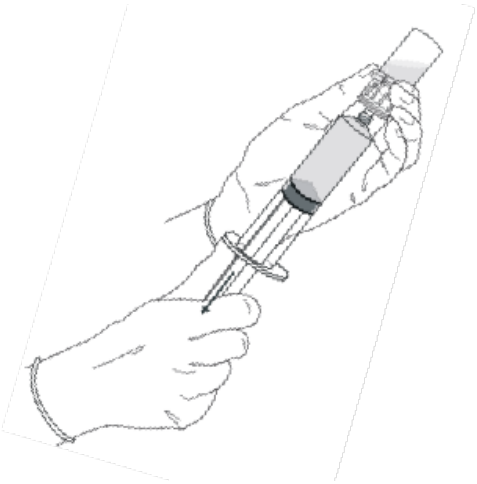


Figure 5

5. Turn the vial up-side down and withdraw all of the dissolved solution from the powder vial back into the syringe (Figure 5).

   The potential to block the venting action exists if large amounts of air or DILUENT are injected when the vial is inverted. If this occurs, turn the vial up right and pull the plunger rod up the syringe barrel.

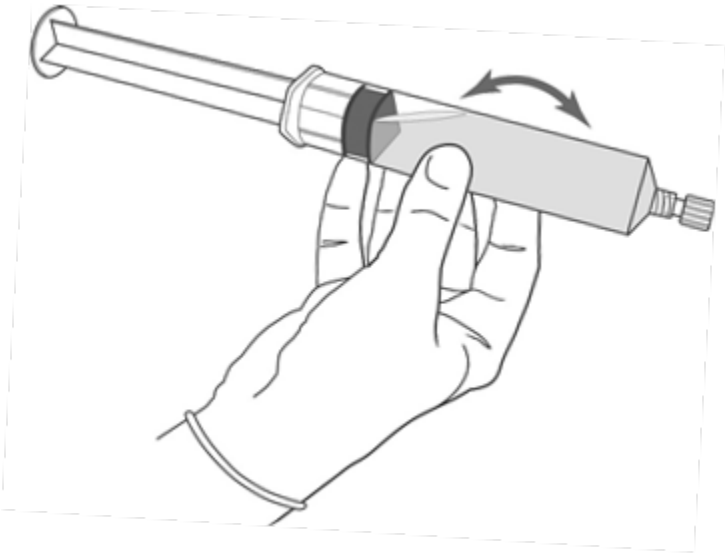


Figure 6

6. Disconnect the empty vial with the vial adapter from the syringe tip and discard it. Plug the syringe with the syringe cap (Figure 6). Gently mix the contents of the syringe. The reconstituted solution of Cysview is colourless to pale yellow and clear to slightly opalescent, and free from visible particles.

7. On the syringe label, write down the date and time of reconstitution. After reconstitution with the DILUENT: If not administered shortly after reconstitution, the solution can be stored for up to 2 hours in a refrigerator between 2 °C–8 °C in the labeled syringe. If not used within 2 hours, the solution must be discarded.

   Cysview is now reconstituted and ready for use.

Vial Size	Volume of DILUENT to be Added to the Vial	Approximate Available Volume	Nominal Concentration of Hexaminolevulinate
10 mL	50 mL	50 mL	1.7 mg/mL (8 mmol/L)

Bladder Instillation of Cysview Solution:

1. Using a standard sterile catheterization technique, insert a urethral catheter into the bladder and completely empty the bladder.

2. Slowly instill 50 mL of the Cysview solution into the bladder, then remove the catheter and instruct the patient to retain the solution within the bladder for at least 1 hour; do not exceed 3 hours. Patients may stand, sit and move about during the time period between instillation and start of the cystoscopic procedure.

3. The patient may void and completely empty the bladder prior to the procedure. If not, evacuate the Cysview solution from the bladder as part of routine emptying of the bladder immediately prior to the initiation of the cystoscopic procedure.

4. Approved cystoscopic equipment with necessary filters to allow both white-light cystoscopy and blue-light (wavelength 360–450 nm) fluorescence cystoscopy should be used. The light doses given during cystoscopy vary depending on the duration of the examination.

Cystoscopic Examination:

Training and proficiency in cystoscopic procedures are essential prior to the use of Cysview. Cysview may not detect all malignant lesions. First perform a complete cystoscopic examination of the entire bladder under white light mode and then repeat the examination of the entire bladder surface under blue light mode 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;
- Malignant lesions may not fluoresce following Cysview administration, particularly if the lesions are coated with necrotic tissue. Blue light may fail to detect T2 tumours which have a tendency to be necrotic on the surface, and necrotic cells generally do not fluoresce;
- When performing the blue-light cystoscopy, avoid prolonged blue light exposure. Studies have not evaluated the potential for adverse effects from blue light.

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.

OVERDOSAGE

No case of overdose with Cysview has been reported.

No adverse events have been reported with instillation times exceeding 180 minutes, in one case 343 minutes. No adverse events have been reported in the dose-finding studies using twice the recommended concentration of hexaminolevulinate.

There is no experience of higher light intensity than recommended or prolonged light exposure.

ACTION AND CLINICAL PHARMACOLOGY

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 cancer cells via 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) [1]. PpIX and PAPs are reported to accumulate preferentially in rapidly dividing neoplastic cells as compared to normal urothelium, partly due to altered enzymatic activity in the neoplastic cells [1,2]. 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 tumour tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Similar processes may occur in inflamed cells.

Pharmacodynamics

In vitro studies have shown a considerable build-up of porphyrin fluorescence in malignant urothelium after exposure to hexaminolevulinate.

In humans, a higher degree of accumulation of porphyrins in lesions compared to normal bladder urothelium has been demonstrated with Cysview. After instillation of the Cysview solution for approximately 60 minutes and subsequent illumination with blue light, tumours can be readily visualized by fluorescence.

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 analysis showed no evidence of significant binding of Cysview to erythrocytes. An *in vitro* study showed that Cysview underwent rapid metabolism in human blood.

Special Populations and Conditions

No adjustments need to be made based on specific subgroups.
Safety and effectiveness in pediatric patients have not been established.

STORAGE AND STABILITY

Store Cysview (hexaminolevulinate HCl), kit for the preparation of intravesical solution, at 15 °C–30 °C. Keep out of reach and sight of children.

The reconstituted solution can be stored under refrigeration (between 2 °C–8 °C) for up to 2 hours in the 50 mL syringe.

SPECIAL HANDLING INSTRUCTIONS

Avoid skin contact with Cysview. If skin does come in contact with Cysview, wash immediately with soap and water and dry off. [See sections WARNINGS AND PRECAUTIONS, Skin, Reconstitution, and TOXICOLOGY].

DOSAGE FORMS, COMPOSITION, AND PACKAGING

Cysview is supplied as a kit labeled Cysview (hexaminolevulinate HCl) 100 mg/vial, kit for the preparation of intravesical solution. Each kit contains:

- 1 vial of Cysview (hexaminolevulinate hydrochloride powder), 100 mg in a 10 mL clear glass vial;
- 1 DILUENT for Cysview, 50 mL in a cyclic olefin copolymer syringe with tip cap, plunger stopper, and plunger rod;
- 1 vial adapter for use during reconstitution.

List of Non-Medicinal Ingredients:

Powder:	None
DILUENT:	Disodium phosphate dihydrate
	Potassium dihydrogen phosphate
	Hydrochloric acid
	Sodium chloride
	Sodium hydroxide
	Water for injections

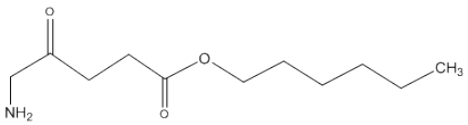
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

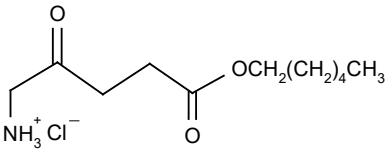
Drug Substance

Common name:	hexaminolevulinate hydrochloride
Chemical name:	hexaminolevulinate hydrochloride
Molecular formula and molecular mass; base:	$C_{11}H_{21}NO_3$, 215.29
Molecular formula and molecular mass; salt:	$C_{11}H_{21}NO_3 \cdot HCl$, 251.76

Structural formula base:



Structural formula salt:



Physicochemical properties: Hexaminolevulinate is provided as a salt; hexaminolevulinate hydrochloride. Hexaminolevulinate hydrochloride is a white to slightly yellow powder. The solubility is 0.8 g/g water. $pK_a = 8.16$. The partition coefficient of hexaminolevulinate hydrochloride in 1-octanol/water has been estimated at log $P_{ow} = 1.68$.

CLINICAL TRIALS

The efficacy of Cysview was established in five phase 3 studies which all included patients with suspected or known non-muscle invasive bladder cancer. One pivotal study, Study B305/04 is presented in this section.

Study demographics and trial design

Study B305/04 was a multi-center, randomized, controlled Phase 3 study investigating the safety and efficacy of Cysview blue-light cystoscopy (BLC) in detection of non-muscle invasive papillary (Ta and T1) bladder cancer. The primary objective was to compare Cysview cystoscopy with white-light cystoscopy (WLC) in the detection of histologically confirmed papillary bladder cancer in patients with papillary bladder cancer.

Eligible patients were randomized to either the WLC group (cystoscopy and TURB under WLC, no Cysview) or the Cysview BLC group (Cysview instillation, cystoscopy under WLC followed by cystoscopy under BLC and TURB under WLC and BLC). Randomization was stratified to ensure an equal distribution of patients with initial and recurrent papillary bladder cancer between the two groups.

The two study groups were well balanced with respect to age, sex, ethnicity, height, and weight. The majority of Intention to treat (ITT) patients in the two study groups were aged 65 years or older (Cysview BLC: 66.6%; WLC: 68.4%), and were male (Cysview BLC: 76.2%; WLC: 78.7%). Almost all patients were white (Cysview BLC: 92.3%; WLC: 95.6%).

Study results

In summary, Cysview BLC was able to detect a significant proportion of Ta or T1 tumours that were not detected with standard WL cystoscopy alone.

The detection primary endpoint was the proportion of Cysview patients with histologically-confirmed tumours (Ta or T1) with at least one such tumour found by Cysview BLC but not by WLC. One of the secondary endpoints was the determination of the proportion of false positive lesions with Cysview BLC and WLC.

Table 3: Ta/T1 Detection Primary Endpoint: Intent-to-treat (ITT) Analysis

Parameter	Cysview Blue-Light Cystoscopy Group n = 365 patients
Number of patients with at least one histologically-confirmed Ta or T1 lesion	286
Number (%) of patients with at least one histologically-confirmed Ta or T1 lesion found by Cysview BLC but not by WLC	47 (16.4%)
(99% CI)	(11.2% – 22.8%)
P-value*	0.0010

CI = Confidence Interval

*p-value from a two-tailed test at a significance level of 0.01 for a difference from 0.1.

In Study B305/04, 16.4% patients had at least one Ta or T1 lesions seen with Cysview BLC that was not seen with WLC, (p = 0.0010).

The false-positive detection rate for Cysview BLC was 12.1%, and the false-positive detection rate for WLC was 10.6% in the Cysview BLC group and 9.8% in the WLC group.

DETAILED PHARMACOLOGY

Non-clinical pharmacokinetics

The *in vivo* pharmacokinetic studies described were performed in the same species and strains that were used in toxicity studies. Except for the radiolabel, the formulations used in the pharmacokinetic studies were similar to those used in toxicity studies. In addition, a pharmacokinetic study using radiolabelled hexaminolevulinate hydrocholoride (HAL HCl) was performed in humans to assess the extent of systemic uptake from the bladder as well as important pharmacokinetic parameters.

While the method of analysing plasma concentrations was validated, the instability of HAL HCl in human plasma and whole blood under all tested storage conditions precluded the determination of systemic exposure after administration. Therefore, [^{14}C]- HAL HCl was used in further studies to allow for the determination of absorption, pharmacokinetics, and distribution of HAL HCl.

A study was also performed to determine the stability of HAL HCl *in vitro* following incubation with human urine at 37°C. During instillation in the bladder, P-1206 (HAL HCl) will be diluted by urine; therefore, the aim of this study was to see if any degradation of P-1206 occurred. It was found that P-1206 was stable over the experimental period; there was little variation in concentration between replicates of urine at each time point; and no clear differences in the concentration of P-1206 between male urine, female urine, or buffer control samples.
The absorption and pharmacokinetics studies using [^{14}C]- HAL HCl were performed in rats and dogs in order to estimate systemic exposure after intravesical administration. Bioavailability of [^{14}C]- HAL HCl was found to be 36% in the rat and 22% in the dog.

An *in vitro* study published by Marti et al[3] showed that the distribution of PAP across the mucosa of porcine and human urinary bladder samples following administration of HAL, 5-aminolevulinic acid (5-ALA) plus desferrioxamine (DES), and 5-ALA alone for 2 hours was largely confined to the urothelium. 5-ALA+DES and especially HAL produced a more homogenous distribution across the urothelium than did 5-ALA.

A study of the distribution of radioactivity was conducted in female Sprague Dawley rats (using quantitative whole-body autoradiography) following a single intravesical administration of [^{14}C]-HAL HCl. These analyses showed that radioactivity was rapidly absorbed and widely distributed but there was apparently no accumulation of radioactivity in any organ or tissue. [^{14}C]-HAL HCl was shown to cross the blood-brain barrier. The IV CNS safety pharmacology study in rats showed signs consistent with an effect on the CNS. The signs included tremor, twitches, increased startle response, changes in locomotor activity and body tone. The signs were noted immediately after dosing and resolved within 60 min after dosing. It is noted that when the dose rate was reduced from bolus to 1 mL/min no signs were noted in animals receiving the intermediate dose of 30 mg/kg indicating a rapid elevation of HAL HCl in the blood was important in the onset of the signs. Elimination was virtually complete within 48 hours after dosing. The majority of the radioactivity was eliminated via the urine (28.4%-34.7%), faeces (17.1%-21.8%), and expired air (16.4%-18.8%). The main metabolite detected in the faeces was unchanged [^{14}C]- HAL HCl.

A metabolism study was conducted to identify selected metabolites of HAL HCl in the plasma of rats following intravesical dosing with [^{14}C]- HAL HCl. Blood samples were collected at 1 hour after dosing, and plasma prepared. The nature of the metabolites of HAL HCl was examined in the plasma samples using radio-HPLC and LC/MS-MS. Reference standards of [^{14}C]- HAL HCl and [^{14}C]-5-ALA were analyzed using this method for comparative purposes. Two major metabolites and several minor metabolites were detected in plasma samples. None of these peaks co-eluted with the reference standards. Both of the major metabolites had a molecular ion weight of 227, but were different in structure. The structures of the metabolites could not be determined, but LC/MS-MS analysis confirmed that the two major metabolites were not ALA or HAL HCl. It was proposed that one peak was identical to the dimerization product P-5007 (2,5-(β-carboxyethyl)dihydropyrazine).

Human pharmacokinetics

A human pharmacokinetic study was performed to determine the extent of systemic absorption of [^{14}C]- HAL HCl following intravesical administration compared with intravenous administration to healthy male volunteers. The mean systemic bioavailability of HAL HCl in humans after intravesical administration for 1 hour was found to be 7% of the instilled dose. Upon analysis of the evacuated urine after a 1-hour instillation of [^{14}C]-labelled HAL HCl, a mean ^{14}C level of 96% was observed, supporting the data for the systemic exposure obtained from plasma measurements. In plasma, [^{14}C]-labelled material showed a biphasic elimination, with an initial elimination half-life of 39 minutes, followed by a terminal half-life of approximately 76 hours.

Human pharmacodynamics

Cysview induces the formation of photoactive porphyrins (PAP) in malignant and premalignant cells in the urothelium when instilled in the bladder. Hexaminolevulinate, the active moiety in Cysview, is an ester of the endogenous early precursor, ALA in the biosynthesis of heme. Exogenously applied hexaminolevulinate leads to the selective formation of PAP 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 fluoresce under illumination with blue light of an appropriate wavelength. It has been shown that the total PAP content increased by a factor of 1.5 with HAL concentrations 2 to 3 orders of magnitude lower than that of ALA in rat bladder transitional carcinoma cells *in vitro*.[4] Thus, HAL may result in a faster rate of PAP build-up in cancer cells *in vivo* as compared to ALA. On the basis of its pharmacological attributes, Cysview was predicted to be effective for the visualization of malignant and premalignant tumours through photodetection.

Marti et al[3,5] have investigated the pharmacology of HAL. In an in vitro study,[3] human and porcine mucosae were exposed to different doses of HAL to investigate the accumulation and distribution of PpIX (the main porphyrin photosensitizer) by microspectrofluorometry. The study showed that the distribution of PAP across the mucosa of porcine and human urinary bladder samples, following the instillation of HAL for 2 hours, was largely confined to the urothelium. HAL produced a homogenous distribution of fluorescence across the urothelium. In an in vivo study,[5] the pharmacokinetics and distribution of PpIX were further investigated in normal and malignant human bladder urothelium in patients with bladder cancer under different dose regimens of HAL. A high PpIX concentration was found in biopsies taken from papillary tumours with much lower levels in the lamina propria, but PpIX was not measurable in the smooth muscle layer.[5]

Another *in vitro* study, study showed that PAP concentration increased with time at pH 5.3 and 6.4, using a 4-mM solution of Cysview. As there were no significant differences in PAP formation between pH 5.3 and 6.4, slight variations in the pH of the instillation solution will have little or no impact on the resulting PAP formation. (The specification range of Cysview ranges from pH 5.7 to 6.2.)

MICROBIOLOGY

Not relevant.

TOXICOLOGY

Studies in rats and dogs have not indicated any risks for systemic toxicity.

Seven-day intravesical tolerance studies, without light exposure, were performed in rats and dogs. The study in rats showed cases of leukocytosis, suggesting a proinflammatory activity of hexaminolevulinate. Cases of azotemia, red coloured urine and weight loss were also seen. In dogs treated with hexaminolevulinate there was a marginally increased incidence and severity of transition cell hyperplasia and basophilia in the urinary epithelium.

A local lymph node assay in mice where Cysview was applied topically to each pinna was performed to assess the antigenicity. The threshold for skin sensitization potential as indicated by the proliferation index is 3. The results as shown in the following table indicate that the proliferation index was in excess of the threshold at doses of ≥10% m/v (≥5 mg/animal). Therefore, HAL was considered to be a moderate to strong sensitizer.

Dose level (% m/v)	10%	25%	50%
Proliferation Index	4.9	18.7	18.6

Potential genotoxicity has been investigated *in vitro* in procaryotic and eucaryotic cells in the presence and absence of photoactivating illumination and *in vivo*. All the studies of genotoxic potential were negative (Ames test, TK assay, *in vivo* micronucleus cell model, chromosome aberrations in CHO cells, and Comet assay on vesical samples from a dog local tolerance study with blue light activation).

Reproductive toxicity has been investigated in rats and rabbits. The incidences of embryo-fetal mortality, fetal weights, and the fetal abnormalities and variants, including skeletal ossification parameters did not indicate any obvious effect of treatment. There were no effects on female fertility and on early embryonic development when investigated in rats.

Carcinogenicity studies have not been performed with hexaminolevulinate.

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PART III: CONSUMER INFORMATION

PrCYSVIEW®

Hexaminolevulinate hydrochloride for intravesical solution
100 mg/vial
Kit for the preparation of intravesical solution

This leaflet is part III of a three-part "Product Monograph" published when Cysview was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Cysview. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

This medicine is used to help identify papillary bladder cancer. It is given before your doctor uses a special device called a 'cystoscope' to look inside of your bladder. A cystoscope helps to see possible tumours, and Cysview helps this process by making the tumour cells illuminate red under blue light, in addition to the usual white light used. After the tumour cells are detected, all the abnormal cells identified under blue light and white light are removed.

What it does:

Cysview is administered into your bladder through a catheter 1 hour before you are sent to the operating room for your cystoscopy examination, and it is taken up by tumour cells in the bladder lining. The tumours then light up in red when the blue light which is provided by the cystoscopic equipment is used in the examination.

When it should not be used:

- If you are allergic (hypersensitive) to the active ingredient or any other ingredients of Cysview (see **What the important non-medicinal ingredients are**);
- If you have 'porphyria' (a rare inherited blood disease).

What the medicinal ingredient is:

Hexaminolevulinate hydrochloride

What the important non-medicinal ingredients are:

Disodium phosphate dihydrate
Potassium dihydrogen phosphate
Hydrochloric acid
Sodium chloride
Sodium hydroxide
Water for injections

What dosage forms it comes in:

Cysview is supplied as a kit labeled Cysview (hexaminolevulinate HCl) 100 mg, kit for the preparation of intravesical solution. Each kit contains:

- 1 vial of Cysview (hexaminolevulinate hydrochloride powder), 100 mg in a 10 mL clear glass vial;
- 1 DILUENT for Cysview, 50 mL in a pre-filled syringe;
- 1 vial adapter.

After mixing, the 50 mL Cysview solution for intravesical solution contains 1.7 mg/mL hexaminolevulinate (8 mmol/L).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Very rare cases of hypersensitivity, including anaphylactic shock, have been reported during post-marketing use of Cysview. Your doctor will have advanced life support facilities available in case of a reaction.

BEFORE you use Cysview, talk to your doctor if:

- You are allergic (hypersensitive) to the active ingredient or any other ingredients of Cysview, including the liquid used to dissolve it;
- You have 'porphyria' (a rare inherited blood disease);
- You are pregnant or planning to become pregnant;
- You are breast-feeding or planning to breast-feed.

The following conditions may cause local reactions in your bladder, which can make it more difficult for your doctor to interpret what he sees during the examination:

- If you have a urinary infection or burning feeling when you pass urine;
- If you have had Bacillus Calmette-Guérin (BCG) therapy or chemotherapy on your bladder less than 90 days ago;
- If you have had an operation on your bladder recently.

This product will be administered by a healthcare professional through a catheter. Cysview is irritating to the skin. In case of accidental contact/spillage of Cysview on the skin, the skin should be washed with soap and water, and dried.

INTERACTIONS WITH THIS MEDICATION

Drug interactions studies have not been done for Cysview. It is not known if any drug may interact with Cysview. Talk to your doctor if you are worried about this.

PROPER USE OF THIS MEDICATION

Usual adult dose:

1 Cysview kit will provide one dose of 50 mL Cysview solution for administration into the bladder by the healthcare professional. The solution will need to stay in your bladder for 1-3 hours. Your doctor (healthcare professional) will monitor your condition for at least 30 minutes after administration of Cysview to watch for allergic reactions.

Overdose:

If Cysview is kept in your bladder for more than 3 hours, no side effects are expected.

If you feel you have been given too much Cysview, speak to your attending healthcare professional for this procedure, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Cysview can cause side effects in some patients. There is a risk of side effects related to the examination technique (cystoscopy) used to look inside of your bladder. The following side effects may happen after blue-light cystoscopy with Cysview.

Common side effects:

Headache, pain and difficulty passing urine, feeling unable to empty your bladder (urinary retention), blood in your urine, pain after the examination (procedure).

If you have severe difficulties or are not able to empty your bladder after you have come home from the hospital, you should contact your physician.

Uncommon side effects:

Feeling sick (nausea), vomiting, diarrhea, constipation, fever (high temperature), burning feeling when you pass urine (caused by inflammation or infection of your bladder), needing to pass urine more often, blood infection, not being able to sleep or difficulty going to sleep, pain in the tube called the 'urethra' that urine passes through, feeling like you need to pass urine right away (urgency), higher levels of white blood cells, increased levels of bilirubin (this is the yellowish pigment in your bile) or increased liver enzymes, these would all be seen in blood test results, lower levels of red blood cells (anaemia), inflammation of the head of the penis (balanitis), back pain, gout, rash.

Frequency not known:

Hypersensitivity reactions (blood pressure drop, increased heart rate, skin rash).

If any of the side effects get serious or have symptoms that you do not understand or find distressing, you should contact your physician immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Contact your doctor	
		Only if severe	In all cases
Common	Feeling unable to empty your bladder (urinary retention)		**X**
	Blood in your urine Pain after the examination (procedure)	**X**	
Uncommon	Fever (high temperature)	**X**	
	Blood infection (chills, rapid breathing, rapid heart rate, confusion, weakness, and red spots on the skin)		**X**
	Burning feeling when you pass urine (caused by inflammation or infection of your bladder) Needing to pass urine more often Pain in the tube called the 'urethra' that urine passes through Feeling like you need to pass urine right away (urgency) Inflammation of the head of the penis (balanitis) Rash	**X**	
Frequency not known	Anaphylactic shock: a severe body reaction with symptoms such as nausea, low blood pressure, fainting, weakness, fast or slow heartbeat, chills, tremor, feeling cold		**X**
	Hypersensitivity (allergic) reaction with symptoms such as itching, rash, hives, swelling of the mouth, throat and extremities, difficulty breathing		**X**

This is not a complete list of side effects. For any unexpected effects while taking Cysview, contact your doctor.

HOW TO STORE IT

Store Cysview (hexaminolevulinate hydrochloride) between 15 °C–30 °C.

If not administered shortly after reconstitution, the healthcare professional will store the solution for up to 2 hours in a refrigerator between 2 °C–8 °C. If not used within 2 hours, the solution will be discarded.

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect
- By calling 1.866.234.2345 (toll-free)
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1.866.678.6789 (toll-free), or
  - Mail to Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.cysview.ca or by contacting the sponsor, Photocure ASA ., at: 1.833-229-1037.

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