PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**CYSVIEW®**

Hexaminolevulinate hydrochloride for intravesical solution

Powder for Solution (kit), 100 mg/vial, Intravesical

Kit for the preparation of intravesical solution

Other diagnostic agents

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	03/2024
4 DOSAGE AND ADMINISTRATION	03/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CYSVIEW (hexaminolevulinate hydrochloride) is indicated for:

As an adjunct to white-light cystoscopy in the diagnosis and follow up of non-muscle invasive bladder cancer, including carcinoma in situ (CIS), in patients with known or suspected bladder cancer to increase tumor detection.

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.

1.1 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 and younger patients.

2 CONTRAINDICATIONS

- Cysview is contraindicated in patients with porphyria. See 7 WARNINGS AND PRECAUTIONS
- 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Very rare cases of hypersensitivity, including anaphylactic shock, have been reported during post-marketing use of Cysview, see 8 ADVERSE REACTIONS. Advanced life support facilities should be readily available.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

No dosing adjustments are required.

4.2 Recommended Dose and Dosage Adjustment

50 mL of the 8 mmol/L Cysview solution (see 4.3 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.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Handling instructions for the pharmacist and 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.

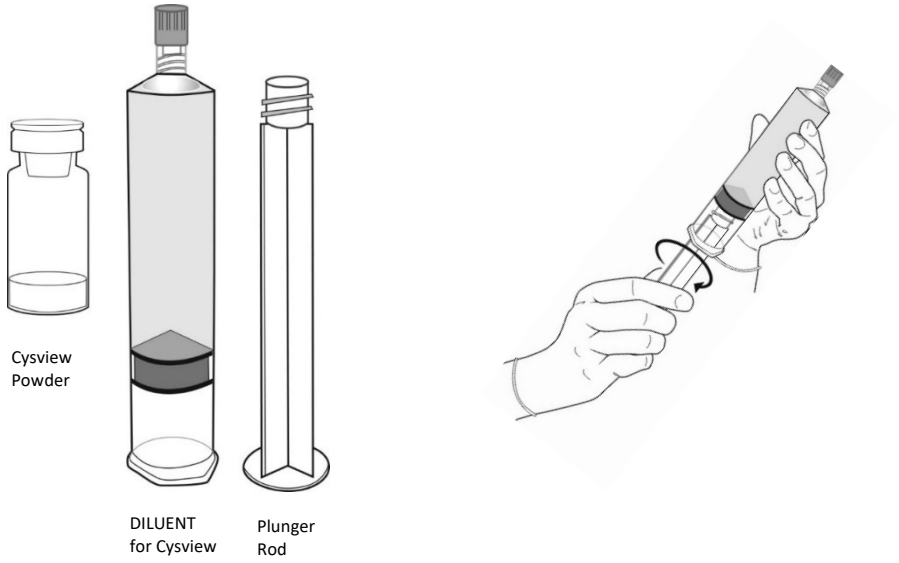


Figure 1

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).

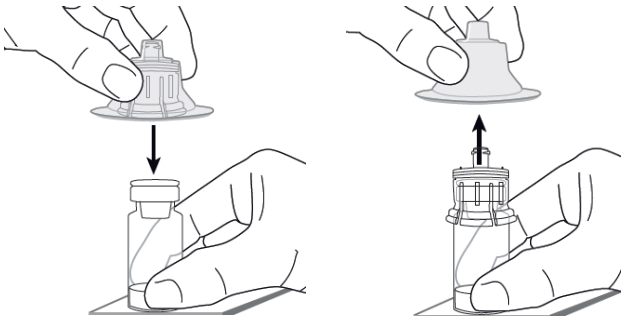


Figure 2

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).

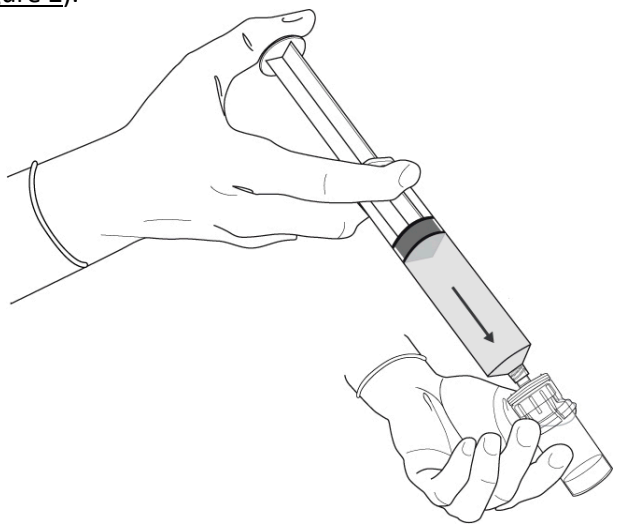


Figure 3

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).

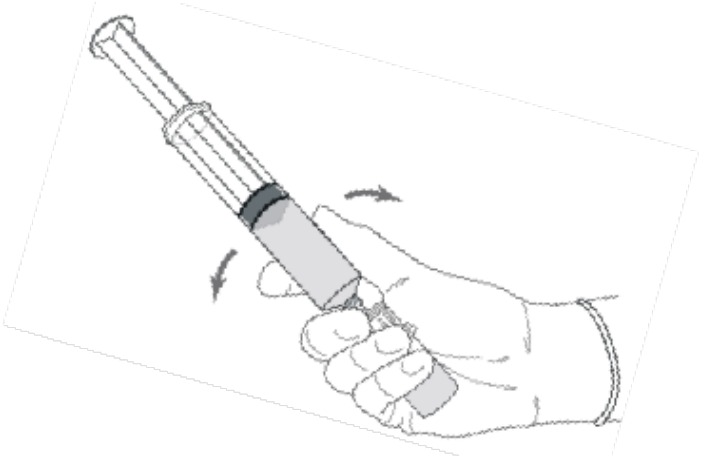


Figure 4

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.

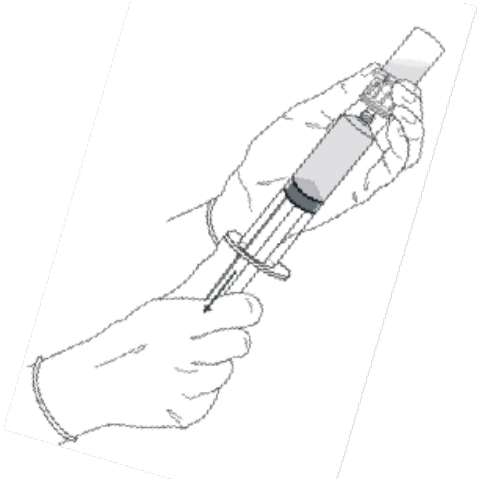


Figure 5

5. Turn the vial upside 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 upright and pull the plunger rod up the syringe barrel.

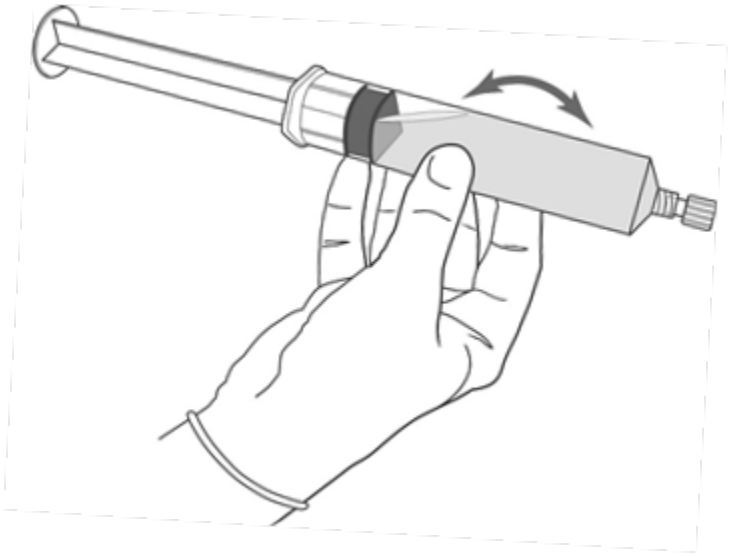


Figure 6

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. Cysview is now reconstituted and ready for use.

   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 in the labeled syringe for up to 2 hours in a refrigerator between 2 °C–8 °C. If not used within 2 hours, the solution must be discarded.

Table 1 - Reconstitution

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

4.4 Administration

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, flat) 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.

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

No case of overdose with Cysview has been reported.

No adverse events have been reported with instillation times exceeding 180 minutes (up to 343 minutes in one case). 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, 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.

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravesical	Cysview 100 mg kit for the preparation of 1.7 mg/mL hexaminolevulinate solution.	Powder: - None DILUENT: - Disodium phosphate dihydrate - Hydrochloric acid - Potassium dihydrogen phosphate - Sodium chloride - Sodium hydroxide - Water for injections

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Please see 16 NON-CLINICAL TOXICOLOGY section. All the studies of genotoxic potential were negative. No long-term studies to evaluate the carcinogenicity potential of Cysview have been performed.

Genitourinary

Do not use in patients with gross hematuria.

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

Immune

Anaphylactoid/hypersensitivity reactions characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock have occurred after Cysview administration, see 8 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.

Peri-Operative Considerations

- **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. False fluorescent areas within the bladder mucosa may result from inflammation, cystoscopic trauma, scar tissue or bladder mucosal biopsy from a previous cystoscopic examination. In the clinical studies, the rate of false positive detection was ranging from 17.3%-43.9% in white light cystoscopy and 21.9-49.1% in blue light cystoscopy. In a study of patients treated with recent BCG immunotherapy or intravesical chemotherapy, the rate of false positives with blue light was 55% between 6 weeks to 90 days and 41% after 90 days; the false positive rate was 53% and 33% at the respective time intervals with white light. See 14 CLINICAL TRIALS.

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.

Reproductive Health: Female and Male Potential

- **Fertility and Teratogenic risk:**

Animal studies do not indicate direct or indirect harmful effects with respect to embryofetal toxicity, teratologic effects or female fertility. See 7.1.1 Pregnant Women

Skin

Cysview may cause sensitisation upon contact with the skin.

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY. Cysview should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is unknown if Cysview is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse 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.

No additional safety risk has been identified by repeated use of Cysview.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In seven clinical trials with CYSVIEW, safety data were obtained from 1,628 patients. Table 3 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 3 Summary of Adverse Reactions Occurring in ≥ 1% of Patients by Body System, Preferred Term and Severity in the Controlled Studies

	Cysview n=1628 Mild (%)	Cysview n=1628 Moderate (%)	Cysview n=1628 Severe (%)	Cysview n=1628 Sum (%)
Injury, poisoning, and procedural complications	**8 (0.5%)**	**16 (1.0%)**	**0 (0.0%)**	**24 (1.5%)**
Procedural pain	6 (0.4%)	14 (0.9%)	0 (0.0%)	20 (1.2%)

	Cysview n=1628 Mild (%)	Cysview n=1628 Moderate (%)	Cysview n=1628 Severe (%)	Cysview n=1628 Sum (%)
Renal and urinary disorders	**58 (3.6%)**	**53 (3.3%)**	**11 (0.7%)**	**109 (6.7%)**
Bladder spasm	19 (1.2%)	9 (0.6%)	4 (0.2%)	32 (2.0%)
Dysuria	14 (0.9%)	12 (0.7%)	0 (0.0%)	26 (1.6%)
Bladder pain	5 (0.3%)	15 (0.9%)	3 (0.2%)	23 (1.4%)
Hematuria	15 (0.9%)	9 (0.6%)	1 (0.1%)	25 (1.6%)
Urinary retention	5 (0.3%)	10 (0.6%)	2 (0.1%)	17 (1.0%)

8.3 Less Common Clinical Trial Adverse Reactions

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, diarrhoea, 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: headache, dizziness, dizziness postural, migraine

Psychiatric disorders: depression, disorientation, insomnia

Renal and urinary disorders: bladder distension, calculus bladder, contracted bladder, incontinence, micturition urgency, nocturia, pollakiuria, urethral pain, 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, dermatitis contact

Vascular disorders: flushing, haemorrhage, hypertension, hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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

8.5 Post-Market Adverse Reactions

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

The drug-related adverse events in Table 4 were reported spontaneously post marketing. Only adverse reactions not already listed in the Clinical Trial Adverse Reactions section, or with changes in severity, frequency or character are listed below.

Table 4: 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
General disorders and administration site conditions	Very rare	Chest discomfort, Chills, Drug ineffective, Feeling hot, Pain
Immune system disorders	Very rare	Anaphylactoid shock, Hypersensitivity
Infections and infestations	Very rare	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, Paresthesia
Renal and urinary disorders	Very rare	Anuria, Bladder irritation, Micturition urgency, Renal pain
Respiratory, thoracic and mediastinal disorders	Very rare	Dyspnoea, Pharyngeal oedema, Pulmonary oedema
Skin and subcutaneous tissue disorders	Very rare	Cold sweat, Cutaneous vasculitis, Erythema, 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.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Hexaminolevulinate hydrochloride (HAL HCL) is an ester of the heme precursor, aminolevulinic acid. After bladder instillation, HAL HCL 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). 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 . 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.

10.2 Pharmacodynamics

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

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

HAL HCL induces the formation of photoactive porphyrins (PAP) in malignant and premalignant cells in the urothelium when instilled in the bladder. Hexaminolevulinate (HAL), the active moiety of the product, is an ester of the endogenous early precursor, ALA in the biosynthesis of heme. Exogenously applied HALleads 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. 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, HAL was predicted to be effective for the visualization of malignant and premalignant tumours through photodetection.

Marti et al have investigated the pharmacology of HAL. In an in vitro study, 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, 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.

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 HAL HCL. 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.)

10.3 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]-labelledHAL 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.

Absorption

After bladder instillation of [^{14}C]-labeled HAL HCL (100 mg) for approximately 1 hour in healthy volunteers, absolute bioavailability of HAL was 7% (90% confidence interval [CI]: 5%-10%).

Distribution:

Whole blood analysis showed no evidence of significant binding of HAL to erythrocytes.

Metabolism:

An in vitro study showed that HAL underwent rapid metabolism in human blood.

Elimination

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.

Special Populations and Conditions

No adjustments need to be made based on specific subgroups.

Safety and effectiveness in pediatric patients have not been established.

11 STORAGE, STABILITY AND DISPOSAL

Store Cysview (hexaminolevulinate hydrochloride), 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 in the 50 mL syringe for up to 2 hours under refrigeration

(between 2 °C–8 °C)

12 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 7 WARNINGS AND PRECAUTIONS, 4.3 Reconstitution, and 16 NON-CLINICAL TOXICOLOGY.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance:

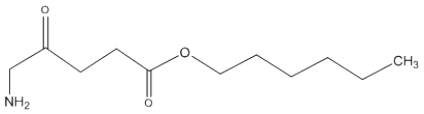
Proper name: hexaminolevulinate hydrochloride

Chemical name: hexaminolevulinate hydrochloride

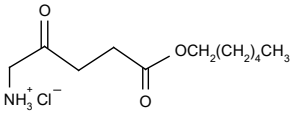
Molecular formula and molecular mass, base: $C_{11}H_{21}NO_3$, 215.29

Molecular formula and molecular mass, salt: $C_{11}H_{21}NO_3$ 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. pKa = 8.16. The partition coefficient of hexaminolevulinate hydrochloride in 1 octanol/water has been estimated at log Pow = 1.68.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The efficacy of Cysview was established in six Phase 3 studies that all included patients with suspected or known non-muscle invasive bladder cancer. Two pivotal studies, Study B305/04 and Study B308/13 are presented in this section.

Study B305/04:

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 5 - Results of study B305/04 in detection of non-muscle invasive papillary (Ta and T1) bladder cancer: 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.

<u>Study B308/13:</u>

The safety and efficacy of Cysview BLC in the detection of bladder cancer during surveillance cystoscopy were studied in a second pivotal prospective, open, comparative within-patient controlled clinical trial. Adult patients with bladder cancer in follow-up for tumor recurrence received Cysview by bladder instillation (n=304). The average age of the patients was 69 years (range 35 to 92); 80% were male and 89% were Caucasian. After bladder evacuation of a standard WLC was performed, followed by Cysview BLC. Of 304 patients, 107 had lesions visually suspected for malignancy based on findings in either Cysview BLC or WLC, of which 103 were referred to the operating room (OR) within 6 weeks for a repetitive Cysview instillation followed by WLC and BLC rigid cystoscopy. In the OR, biopsies were taken to confirm malignancy and the suspicious lesions were surgically removed by TURB. Pathological evaluation was performed by a centralized blinded panel.

Efficacy of Cysview BLC in the surveillance setting was assessed in this study as the proportion of patients with histologically confirmed malignancy where malignancy was only detected with CYSVIEW BLC and not WLC. The proportion was compared to a proposed threshold value of 0.5%. Of 103 patients, 63 had at least one confirmed malignant lesion, including 13 (20.6%, p<0.0001) patients with malignancy detected only by Cysview BLC, 1 (1.6%) patient who had malignancy detected only with WLC, and 49 (77.8%) patients with malignancy detected by both Cysview BLC and WLC.

Efficacy of Cysview BLC in the detection of CIS was evaluated in this study as the proportion of patients with one or more CIS lesions detected with Cysview BLC and none with WLC. The assessment compared lesions detected during the cystoscopic examination in the OR to the pathological findings. The proportion of these patients was compared to a proposed threshold value of 0.1%. Of the 63 patients with confirmed lesions, 26 patients had at least one CIS lesion, including 9 (34.6%, p<0.0001) patients who had at least one of the CIS lesions detected only by Cysview BLC and none by WLC. Two patients had at least one CIS lesion detected only by WLC and none by Cysview BLC, and 15 patients had CIS-lesions detected by both Cysview BLC and WLC.

Some patients had suspected lesions at time of the surveillance examination, that later showed no malignancy (false positives). Of the 103 evaluable patients, 20 had false positive lesions seen only with Cysview BLC (19.4%; 95% CI: 12.3% to 28.4%). In comparison, three patients had false positive lesions seen only with WLC (2.9%; 95% CI: 0.6% to 8.3%). Seventeen patients (16.5%) had false positive lesions seen with both Cysview BLC and WLC.

There were 315 lesions detected during the cystoscopy in the OR. Table 6 shows the detection of lesions by type of malignancy, including false positive detection.

Table 6 - Lesion Detection by Type of Malignancy as Verified in the OR

Malignancy Type	Detected by Both WL & BL	Detected by WL Only	Detected by BL Only
CIS, n = 43	24	3	16
Ta, n = 94	61	9	24
T1, n = 10	7	0	3
T2 – T4, n = 5	5	0	0
PUNLMP** n=3	2	0	1
False positive n=160	65	22	73
Total number of lesions	164	34	117

** papillary urothelial neoplasm of low malignant potential

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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

Carcinogenicity: Carcinogenicity studies have not been performed with hexaminolevulinate.

Genotoxicity: Potential genotoxicity has been investigated in vitro in prokaryotic and eukaryotic 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 and Developmental Toxicology: 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.

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, HAL HCl will be diluted by urine; therefore, the aim of this study was to see if any degradation of HAL HCl occurred. It was found that HAL HCl 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 HAL HCl 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 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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCYSVIEW®

Hexaminolevulinate hydrochloride for intravesical solution

100 mg/vial

Kit for the preparation of intravesical solution

Read this carefully before you start taking **Cysview** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Cysview**.

Serious Warnings and Precautions
Very rare cases of hypersensitivity (allergic reaction), including anaphylactic shock, have been reported when using Cysview. Tell your healthcare professional if you think you might be experiencing an allergic reaction during your procedure.

What is Cysview used for?

This medicine is used to help identify 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. The medicine is used in addition to the usual white light procedure. After the tumour cells are detected, all the abnormal cells identified under blue light and white light are removed.

How does Cysview work?

Cysview is administered into your bladder through a catheter 1 hour before you are sent to the operating room for your cystoscopy examination. This allows Cysview to be taken up by tumour cells in the bladder lining. The tumours then light up in red when your doctor switches the cystoscopic equipment being used to the blue light mode.

What are the ingredients in Cysview?

Medicinal ingredients:	Hexaminolevulinate hydrochloride
Non-medicinal ingredients:	Disodium phosphate dihydrate
	Hydrochloric acid,
	Potassium dihydrogen phosphate
	Sodium chloride
	Sodium hydroxide
	Water for injections

Cysview comes in the following dosage forms:

Cysview is supplied as a kit labeled "Cysview (hexaminolevulinate hydrochloride) 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.

Do not use Cysview if:

- You have 'porphyria' (a rare, inherited blood disease);
- You are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the "What are the ingredients in Cysview?" section.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cysview. Talk about any health conditions or problems you may have, including if you:

- Can see blood in your urine;
- Are pregnant or planning to become pregnant;
- Are breast-feeding or planning to breast-feed.

Other warnings you should know about:

The following conditions may cause local reactions in your bladder, which can make it more difficult for your healthcare professional to interpret what he/she see 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 fewer than six weeks ago;
- If you have had an operation on your bladder recently.

This product will be administered by a healthcare professional through a catheter. Cysview may be 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Cysview:

- Cysview will be given to you by a healthcare professional through a catheter before your procedure.
- Your healthcare professional will monitor your condition for at least 30 minutes after administration of Cysview to watch for allergic reactions.

Usual dose:

One 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.

Overdose:

If you think you, or a person you are caring for, have been given too much Cysview, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Cysview?

These are not all the possible side effects related to use of Cysview that you may have. If you experience any side effects not listed here, tell your healthcare professional.

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:

- Feeling sick (nausea);
- vomiting;
- diarrhoea;
- constipation.

Uncommon side effects:

- Headache
- not being able to sleep or difficulty going to sleep;
- 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),
- back pain;
- gout.

Serious Side Effects and What To Do About Them			
Symptom / Effect	**Talk to Your Healthcare Professional**		**Stop taking drug and get immediate medical help**
	Only if Severe	**In All Cases**	
COMMON			
Feeling unable to empty your bladder (urinary retention)		X	
Blood in your urine	X		
Pain after the examination (procedure)	X		
Fever (high temperature)	X		
RARE			
Blood infection (chills, rapid breathing, rapid heart rate, confusion, weakness, or red spots on the skin)		X	

Serious Side Effects and What To Do About Them			
Symptom / Effect	**Talk to Your Healthcare Professional**		**Stop taking drug and get immediate medical help**
	Only if Severe	**In All Cases**	
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, itching	X		
VERY RARE			
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	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

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.

If you want more information about Cysview:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.cysview.ca, or by calling 1-833-229-1037.

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