INDICATIONS AND USAGE
Cysview (hexaminolevulinate hydrochloride) is supplied as a kit. The kit may be supplied as two options; with or without a vial adapter:
- One 10 mL glass vial containing 100 mg powder of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution.
- One plastic prefilled syringe containing 50 mL DILUENT for Cysview.
- One Luer Lock catheter adapter.
- One vial adapter for use during reconstitution (in the kit containing the vial adapter). (16)
Once reconstituted, the solution contains 2 mg/mL (8 mmol/L) of hexaminolevulinate hydrochloride.

CONTRAINDICATIONS
Do not use Cysview in patients with:
- porphyria,
- gross hematuria,
- known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives. (4)

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

ADVERSE REACTIONS
The most common adverse reaction reported in patients who received Cysview was bladder spasm, occurring in 2% of patients, followed by dysuria, hematuria and bladder pain. (6.1)

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

USE IN SPECIFIC POPULATIONS
Pediatric Use: Safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.
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 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).

3. Remove the cap from the prefilled syringe and carefully retain it for subsequent reattachment to the syringe. Hold the prefilled 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 prefilled syringe down into the vial. The vial should be about ¾ full (Figure 3).

4. Turn the vial up-side down and withdraw all of the dissolved solution from the vial back into the syringe (Figure 4). Do not inject large amounts of air or diluent when vial is inverted as it may block the venting action of the vial adapter. If this occurs, turn the vial up right and pull back on the plunger rod in the syringe.

5. Turn the vial up-side down and withdraw all of the dissolved solution from the vial back into the syringe (Figure 5). Do not inject large amounts of air or diluent when vial is inverted as it may block the venting action of the vial adapter. If this occurs, turn the vial up right and pull back on the plunger rod in the syringe.

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 colorless to pale yellow and clear to slightly opalescent, and free from visible particles. Cysview is now reconstituted and ready for use. The solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride. Instill the reconstituted solution of Cysview into the bladder (see Bladder Instillation of Cysview (2.3)). If unable to administer the solution shortly after reconstitution, store the solution for up to 2 hours in a refrigerator at 2°-8°C (36°-46°F) in the labeled syringe. If not used within 2 hours, discard the solution [see How Supplied/Storage and Handling (16)].

7. Peel off the detachable portion of the syringe label. On the syringe label, add two hours to the present time and write the resulting expiration time and date. Cysview is now reconstituted and ready for use. The solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride. Instill the reconstituted solution of Cysview into the bladder [see Bladder Instillation of Cysview (2.3)]. If unable to administer the solution shortly after reconstitution, store the solution for up to 2 hours in a refrigerator at 2°-8°C (36°-46°F) in the labeled syringe. If not used within 2 hours, discard the solution [see How Supplied/Storage and Handling (16)].

Reconstitution Without the Use of a Vial Adapter

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

2. Remove the plastic cap from the vial. Remove the cap from the prefilled syringe and carefully retain it for subsequent reattachment to the syringe. Attach a needle to the prefilled syringe. Hold the prefilled syringe upright and carefully press the plunger rod upward to remove air. Penetrate the stopper of the Cysview vial with the needle and inject about 10 mL of the diluent from the prefilled syringe down into the vial. The vial should be about ¾ full (Figure 7).

3. Without withdrawing the needle from the vial, hold the vial and syringe in a firm grip (Figure 8) and gently shake to dissolve of the powder in the diluent. The powder normally dissolves almost immediately.

4. Remove the needle from the vial, disconnect the needle from the syringe tip and discard it. Plug the syringe with the syringe cap (Figure 10). Gently mix the contents of the syringe. The reconstituted solution of Cysview is colorless to pale yellow and clear to slightly opalescent, and free from visible particles.

5. Remove the needle from the vial, disconnect the needle from the syringe tip and discard it. Plug the syringe with the syringe cap (Figure 10). Gently mix the contents of the syringe. The reconstituted solution of Cysview is colorless to pale yellow and clear to slightly opalescent, and free from visible particles.

6. Peel off the detachable portion of the syringe label. On the syringe label, add two hours to the present time and write the resulting expiration time and date. Cysview is now reconstituted and ready for use. The solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride. Instill the reconstituted solution of Cysview into the bladder [see Bladder Instillation of Cysview (2.3)]. If unable to administer the solution shortly after reconstitution, store the solution for up to 2 hours in a refrigerator at 2°-8°C (36°-46°F) in the labeled syringe. If not used within 2 hours, discard the solution [see How Supplied/Storage and Handling (16)].

2.3 Bladder Instillation of Cysview

For bladder instillation of the solution of Cysview, use straight, or intermittent, urethral catheters with a proximal funnel opening that will accommodate the Luer Lock adapter. Use only catheters made of vinyl (uncoated or coated with hydrogel), latex (amber or red), and silicone to instill the reconstituted Cysview. Do not use catheters coated or embedded with silver or antibiotics. In-dwelling bladder catheters (Foley catheters) may be used if the catheters are inserted shortly prior to Cysview administration and are removed following the Cysview instillation.

Use the following steps for bladder instillation of Cysview:

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

2. To attach the syringe containing the solution of Cysview to the catheter, do the following:
   - Remove the syringe cap from the syringe that contains the reconstituted solution of Cysview.
   - Attach the Luer Lock end of the (provided) catheter adapter to the syringe.
   - Insert the tapered end of the catheter adapter into the funnel opening of the catheter. See Figure 11, with the connection enlarged in the inset.

3. Slowly instill the solution of Cysview into the bladder through the catheter (Figure 11), ensuring that the complete volume of the syringe (50 mL) is administered.

4. After the solution is instilled, remove the catheter and instruct the patient to retain the solution within the bladder for at least 1 hour; do not exceed 3 hours [see Cystoscopic examination (2.5)]. Patients may stand, sit and move about during the time period between instillation and start of the cystoscopic procedure.

5. Evacuate the solution of Cysview from the bladder as part of routine emptying of the bladder immediately prior to the initiation of the cystoscopic procedure (refer to the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) System Manual for further details). Also, the patient may void and completely empty the bladder prior to the procedure.

Avoid skin contact with Cysview. If skin does come in contact with Cysview, wash immediately with soap and water and dry off. After voiding the bladder of Cysview, routinely wash the patient’s perineal skin region with soap and water and dry.
5.3 False Positive Fluorescence
Fluorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. In the controlled clinical studies, approximately 20% of the lesions detected only by blue light cystoscopy showed no evidence of dysplasia nor carcinoma [see Clinical Studies (14)]. False positive fluorescence may result from inflammation, cystoscopic trauma, scar tissue or bladder mucosal biopsies from a previous cystoscopic examination, and recent BCG immunotherapy or intravesical chemotherapy. In a study of patients treated with recent BCG immunotherapy or intravesical chemotherapy, the rate of false positives with white light was 55% between 6 weeks to 90 days and 41% after 60 days; the false positive rate was 53% and 33% at the respective time intervals with white light.

The presence of urine and/or blood within the bladder may interfere with the detection of tissue fluorescence. To enhance the diagnostic utility of Cysview with the KARL STORZ D-Light C PDD System:
• ensure the bladder is emptied of urine prior to the instillation of fluids at cystoscopy;
• biopsy/resect bladder mucosal lesions only following completion of both white light and blue light cystoscopy.

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

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

In seven clinical trials, safety data were obtained from 1,628 patients, aged 32 to 96 years with a median age of 70 years, all primarily Caucasian and approximately 75% male. All patients were evaluated after a single instillation of 50 mL solution of Cysview, and 163 patients received a repeat administration of Cysview. Of these patients, 170 (10.4%) patients reported at least one adverse reaction. The most common adverse reaction was bladder spasm (reported in 2.0% of the patients) followed by dysuria, hematuria, and bladder pain. No patients experienced anaphylaxis. In the randomized controlled clinical study, adverse reactions were similar in nature and rate between the study drug group and the control group. In a controlled study using Cysview in the surveillance setting, adverse reaction types were similar [see Clinical Studies (14)].

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Cysview. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

7 DRUG INTERACTIONS
No specific drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Cysview use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Adequate reproductive and developmental toxicity studies in animals have not been performed. Systemic absorption following administration of Cysview is expected to be minimal [see Clinical Pharmacology (12.3)].

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary
There are no data on the presence of hexaminolevulinate in human or animal milk, the effects on a breastfed infant, or the effects on milk production. Systemic absorption following administration of Cysview is expected to be minimal [see Clinical Pharmacology (12.3)]. The lack of clinical data during lactation precludes a clear determination of the risk of Cysview to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Cysview and any potential adverse effects on the breastfed infant from Cysview or from the underlying maternal condition.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Of 2127 subjects in clinical studies of Cysview, 67% were 65 years and over. No clinically important differences in safety or efficacy have been observed between older and younger patients in the controlled study.

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

11 DESCRIPTION
Cysview contains hexaminolevulinate hydrochloride, an optical imaging drug that in solution form is instilled intravesically for use with photodynamic blue light cystoscopy as an adjunct to white light cystoscopy. The chemical formula for hexaminolevulinate hydrochloride is C11H21N3O3 HCl. Its molecular weight is 251.76 and it has the following structural formula:

\[
\text{Cysview (hexaminolevulinate hydrochloride) for Intralesional Solution is intended for intravesical administration only after reconstitution with the supplied 50 mL DILUENT. Cysview (hexaminolevulinate hydrochloride) for Intralesional Solution and DILUENT for Cysview are supplied together as a kit.}
\]

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

The reconstituted solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride and is colorless to pale yellow. It is free from visible particles and has a pH between 5.7 and 6.2.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In vitro studies have shown increased porphyrin fluorescence in normal urothelium after exposure to Cysview. In the human bladder, a greater accumulation of porphyrin is proposed in neoplastic or inflamed cells, compared to normal urothelium. After bladder instillation of Cysview for approximately 1 hour and subsequent illumination with blue light at wavelengths 360 – 450nm, the porphyrins will fluoresce red [see Dosage and Administration (2.5)].

12.3 Pharmacokinetics

After bladder instillation of [14C]-labeled Cysview (100 mg) for approximately 1 hour in healthy volunteers, absolute bioavailability of Cysview was 7% (90% confidence interval [CI]: 5% - 10%). The [14C]-labeled substance(s) exhibited 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.

13 NONCLINICAL TOXICLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies in animals have been conducted to evaluate the carcinogenic potential of hexaminolevulinate hydrochloride. Hexaminolevulinate hydrochloride was not mutagenic in in vitro reverse mutation tests in bacteria, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an in vivo micronucleus test in mice after intravenous injection of doses up to 45 mg/kg in the absence of light activation. Adequate studies have not been performed to evaluate the genetic toxicity of hexaminolevulinate hydrochloride in the presence of light activation.

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

The safety and efficacy of Cysview when used with photodynamic cystoscopy were studied in two controlled clinical trials.

Study 1: A prospective, multicenter, controlled clinical trial in adult patients with known or suspected bladder cancer who were randomized to either white light (WL) cystoscopy (control group, n = 384) or WL followed by blue light (BL) cystoscopy (study drug group, n = 390). Only the study drug group patients received Cysview by bladder instillation prior to cystoscopy. After bladder evacuation of Cysview, bladder lesion mapping was performed initially using the KARL STORZ PDD system in the WL mode followed by lesion mapping in the BL mode. Control group patients underwent only WL cystoscopy with lesion mapping. The average age of the randomized patients was 69 years (range 24 to 96); 78% were male and 94% were Caucasian. All patients had had malignancy detected by both WL and BL; 1 patient had malignancy detected by WL only; and 13 patients had malignancy detected by BL only [12.6% with 95% CI (7%, 21%), p<0.0001]. Among these 103 patients, 40 patients had false positive detections: 17 patients had false positive detection by both WL and BL; 3 patients had false positive detection by WL only; and 20 patients had false positive detection by BL only.

In the same study, there were 315 lesions detected during the cystoscopy in the OR. Table 4 shows the detection of lesions by type of malignancy.

Table 4: Lesion Detection by Type of Malignancy as Verified in the OR

<table>
<thead>
<tr>
<th>Malignancy Type</th>
<th>Detected by Both WL &amp; BL</th>
<th>Detected by WL Only</th>
<th>Detected by BL Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS, n = 43</td>
<td>24</td>
<td>3</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Ta, n = 94</td>
<td>61</td>
<td>0</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>T1, n = 10</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>T2 – T4, n = 5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PUNL/MCP, n = 3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>False positive, n=160</td>
<td>85</td>
<td>22</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Total number of lesions</td>
<td>164</td>
<td>34</td>
<td>117</td>
<td></td>
</tr>
</tbody>
</table>

*Suprapubic urethral resection of low malignant potential

16 HOW SUPPLIED/STORAGE AND HANDLING

Cysview is supplied as a kit labeled Cysview (hexaminolevulinate HCl) Kit for Intravesical Solution, 100 mg. The kit may be supplied as two options; with or without a vial adapter, and contains:

- Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg, as a powder in a 10 mL clear glass vial.
- One plastic prefilled syringe of DILUENT for Cysview, 50 mL.
- One vial adapter for use during reconstitution. The vial adapter is either a “West Ventilating Vial Adapter” or a “West Mixject Dispensing Pin”.
- One Luer Lock catheter adapter (to connect the syringe containing the reconstituted solution of Cysview to the urethral catheter for bladder instillation of Cysview).

NDC 10511-3001-2

Cysview kit without a vial adapter

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

NDC 10511-3001-3

Storage

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

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

17 PATIENT COUNSELING INFORMATION

Ask patients if they have:
- a diagnosis or a family history of porphyria, allergy to aminoacetic acid or prior exposure to Cysview, or grass hay fever.
- had BCG immunotherapy or chemotherapy within the bladder.

Inform patients that Cysview should be retained in the bladder for 1 hour from instillation of Cysview to the start of the cystoscopic procedure. If the patient cannot hold Cysview for 1 hour but needs to void and expel Cysview from the bladder, he or she may void and should then inform a health care professional [see Dosage and Administration (1.7)].

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