



Lynda Sutton, U.S. Agent
Photocure ASA
c/o Cato Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

RE: NDA 022555
Cysview (hexaminolevulinate hydrochloride), for Intravesical Solution
MA #14

Dear Ms. Sutton:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the "Patient guide to Cysview blue light cystoscopy for detection of bladder cancer" (CYSC2012004) (patient guide) for Cysview (hexaminolevulinate hydrochloride), for Intravesical Solution (Cysview), submitted by Photocure ASA (Photocure) under cover of Form FDA-2253. The patient guide is false or misleading because it omits and minimizes risk information, and makes unsubstantiated superiority claims for Cysview. Therefore, the patient guide misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a); 321(n). Cf. 21 CFR 202.1(e)(5)(i), (iii) & (e)(6)(ii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Cysview.¹

According to its FDA-approved product labeling (PI) (emphasis original):

Cysview is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1).

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Limitations of Use

Cysview is not:

- a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer
- for repetitive use. The potential risks associated with repetitive exposure, including sensitization and adverse effects of blue light have not been evaluated.

Cysview is contraindicated in patients with porphyria, gross hematuria, BCG immunotherapy or intravesical chemotherapy within the past 90 days, or known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives.

The PI for Cysview includes WARNINGS AND PRECAUTIONS for anaphylaxis, failed detection of some bladder tumors including malignant lesions, and the possibility of false fluorescence. In addition, the most common adverse reactions reported with Cysview use were bladder spasm, dysuria, hematuria, bladder pain, procedural pain, urinary retention, and headache.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Promotional materials are also misleading if they contain a representation or suggestion that a drug is safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience.

The patient guide includes several efficacy claims and presentations for Cysview; however, it fails to include the important contraindication for patients with gross hematuria. According to the CONTRAINDICATIONS section of the PI, “Cysview is contraindicated in patients with: . . . gross hematuria . . .” Failure to disclose this information suggests that Cysview is safer than has been demonstrated by substantial evidence or substantial clinical experience and is therefore misleading.

Page five of the patient guide includes the following claim:

- “Safety and effectiveness have not been established in patients receiving intravesical chemotherapy or BCG treatment within 3 months of Cysview photodynamic blue light cystoscopy . . .”

This claim misleadingly minimizes the risks of Cysview because it fails to characterize these risks as contraindications, thereby suggesting that the drug is safer than has been demonstrated. Specifically, the CONTRAINDICATIONS section of the PI states, “Cysview is contraindicated in patients with: . . . BCG immunotherapy or intravesical chemotherapy within the past 90 days.” Failure to explicitly communicate that Cysview should not be used in these patients minimizes the risks associated with Cysview and is therefore misleading.

The patient guide includes the following claims and presentations:

- “Under conventional white light, tumors can be virtually invisible and are easily missed. Cysview is taken up faster by malignant cells, causing them to appear first under the blue light, making them easier to see.” (page 6)
- “How your healthcare professional sees images during a Cysview blue light cystoscopy”
(accompanied by side-by-side images of tumors as detected by standard white light cystoscopy and compared to vivid fluorescent images detected by Cysview blue light cystoscopy) (page 7)

These claims and presentations misleadingly minimize the risks associated with Cysview because they fail to disclose the risk of false fluorescence associated with its use. Specifically, according to the WARNINGS AND PRECAUTIONS section of the PI, “[f]luorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. . . . 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.” Failure to disclose the risk of false fluorescence in light of the claims and presentations made in the patient guide minimizes the risks associated with Cysview and is therefore misleading.

Page five of the patient guide includes the following claims (emphasis added):

- “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 possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of anaphylactoid shock, bladder pain, cystitis and abnormal urinalysis have uncommonly been reported.”

The above claims misleadingly minimize the risks associated with Cysview by downplaying and dissociating the serious risk of anaphylaxis. Specifically, although the WARNINGS AND PRECAUTIONS section of the PI states, “[a]naphylaxis, including anaphylactoid shock, has been reported following administration of Cysview,” the patient guide diminishes the severity of this risk by presenting it **only as a postmarketing adverse event that may be unrelated to the drug.**

Additionally, the characterization in the above presentation of “bladder pain” as a risk that has “uncommonly been reported” only during post-approval use of Cysview misleadingly minimizes this risk associated with the drug. Specifically, the ADVERSE REACTIONS section of the PI reports bladder pain among the most common adverse reactions observed during the clinical trials for Cysview. Therefore, the characterization of bladder pain as an uncommon adverse reaction potentially unrelated to the drug misleadingly suggests that Cysview is safer than has been demonstrated. We acknowledge that bladder pain is also included in the listing of the “most common patient complaints” on page six of the patient guide; however this does not mitigate the misleading minimization of risk in the above presentation.

The patient guide includes the following claims (emphasis added):

- “The most common patient complaints include: . . . **pinkish tinge** to the urine . . .” (page 6)
- “A **pinkish tinge** to the urine also is common for several days after the procedure, particularly if you have had some treatment.” (page 8)
- “If your urine still has a **pinkish tinge** . . .” (page 9)

These claims misleadingly minimize the severity of the common adverse event of hematuria associated with Cysview by describing it in terms that patients may not necessarily equate to hematuria. Specifically, the imagery on page seven of the patient guide illustrates that Cysview is taken up by cancerous bladder cells that emit a pink fluoresce when exposed to blue light. The misleading implication of these claims is exacerbated by the fact that the procedure is designed to make areas of concern show pink under observation, thereby adding to the likelihood that patients will interpret pinkish urine as a byproduct of the Cysview blue light cystoscopy, rather than a pink color caused by blood in their urine. Therefore, characterizing the risk of hematuria as “pinkish tinge to the urine,” as opposed to informing patients that they may see blood in their urine, misleadingly suggests that the drug is safer than has been demonstrated.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. Page six of the patient guide includes the following claims (bolded emphasis original, underlined emphasis added):

- “**Why would my doctor order a Cysview blue light cystoscopy instead of the conventional cystoscopy procedure?**

Under certain circumstances, a conventional cystoscopy may provide unclear results. To improve diagnostic accuracy, your healthcare professional may request Cysview blue light cystoscopy.

Under conventional white light, tumors can be virtually invisible and are easily missed. Cysview is taken up faster by malignant cells, causing them to appear first under the blue light, making them easier to see”

These claims misleadingly suggest that Cysview blue light cystoscopy is more effective than traditional white light cystoscopy in the absence of substantial evidence or substantial clinical experience. The suggestion that tumors depicted under traditional white light cystoscopy are “unclear,” “virtually invisible,” and “easily missed,” whereas tumors depicted under Cysview blue light cystoscopy are “easier to see,” with “improve[d] diagnostic accuracy” implies that Cysview blue light cystoscopy is superior to traditional white light cystoscopy when this is not the case. On the contrary, conventional white light cystoscopy detects the majority of bladder tumors, while the primary advantage of Cysview blue light cystoscopy is the potential detection of some bladder tumors not visualized during conventional white light cystoscopy, hence its adjunctive role. In fact, conventional white light cystoscopy detects some tumors

missed by Cysview blue light cystoscopy. The CLINICAL STUDIES section of the PI states that in the pivotal study for Cysview, patients were randomized to either white light cystoscopy, or white light followed by blue light cystoscopy, thereby supporting the FDA-approved indication for use of Cysview blue light cystoscopy as an adjunct to traditional white light instead of a superior alternative. FDA is not aware of substantial evidence or substantial clinical experience to support any suggestion that Cysview blue light cystoscopy, when used alone, demonstrates superior efficacy over traditional white light cystoscopy. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

The patient guide is false or misleading because it omits and minimizes risk information, and makes unsubstantiated superiority claims for Cysview. Therefore, the patient guide misbrands the drug in violation of the FD&C Act, 21 U.S.C. 352(a); 321(n). Cf. 21 CFR 202.1(e)(5)(i), (iii) & (e)(6)(ii).

OPDP requests that Photocure immediately cease the dissemination of violative promotional materials for Cysview such as those described above. Please submit a written response to this letter on or before March 18, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Cysview that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA # 14 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Cysview comply with each applicable requirement of the FD&C Act.

Sincerely,

{See appended electronic signature page}

Adora Ndu, Pharm.D.
LCDR, USPHS
Regulatory Review Officer
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, Pharm.D., RAC, CPA
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/s/

ADORA NDU
03/04/2013

AMY TOSCANO
03/04/2013