

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022555Orig1s000

OTHER ACTION LETTER(s)



NDA 022555

COMPLETE RESPONSE

Cato Research, Ltd. (for Photocure ASA)
Attn: Lynda Sutton, Chief Regulatory Officer
4364 S. Alston Ave.
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated June 30, 2009, received June 30, 2009, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Hexaminolevulinate Hydrochloride *Kit* For Intravesical Solution as a part of a combination product in association with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system, which is the subject of a premarket application (PMA).

We acknowledge receipt of your amendments dated August 20, 25; September 8, 15, 22; October 1, 6, 13, 15, 21, 22, 23, 29; November 4, 9, 19, 20; December 9, 16, 17, and 22, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

REGULATORY

1. Your product, Hexaminolevulinate Hydrochloride *Kit* For Intravesical Solution, is proposed for use in combination with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system. The Karl Storz D-Light C PDD system is the subject of a PMA, which is currently under review by the Center for Devices and Radiological Health (CDRH). FDA cannot approve your NDA until the PMA for the Karl Storz D-Light C PDD system is approved or otherwise ready for approval. We encourage you to work with the manufacturer of the Karl Storz D-Light C PDD system to obtain marketing approval.

CLINICAL

2. Your proposed product vial packaging and product reconstitution procedures do not sufficiently minimize the risk of medication errors. As described in the proposed labeling, (b) (4) the healthcare provider must manipulate a 50 or 60-cc syringe with its attached needle still inserted in the vial. The health care provider then holds the syringe/needle and vial while shaking the contents. These procedures and the resulting unstable connection between the needle and vial are not consistent with usual reconstitution procedures. In addition, these procedures promote unintentional needle puncture/sharps-injury to the healthcare provider. For these reasons, redesign the product packaging configuration and product reconstitution procedures to include a more intuitive process in order to minimize the potential for medication errors or sharps-injury to the provider. Specifically:
 - a. Redevelop your product's reconstitution and preparation process to one that does not involve multiple punctures of the product-powder vial or imply the need for multiple punctures, as may occur with a multi-step reconstitution process. A one step dilution process is preferable and should be supported by the appropriate data. Additionally, the revised process must not involve the use of a needle-appended syringe during the step at which the provider is to (b) (4). Furthermore, your revision should take into consideration any potential failure modes that may occur at all steps of the product reconstitution and preparation process. In addition, as further described in item 4 below, the dilution process should include a method to transfer the final solution to the bladder catheter. Within your submission, include information to support the relationship of the revised dilution-transfer process to, and its consistency with, the process used in the major clinical trials. We encourage a pre-submission meeting to discuss your proposed changes and the appropriate testing to ensure the usability of the revised product packaging configuration and preparation procedures by the appropriate end-users. In developing your system we recommend consideration of principles in the FDA Guidance: *Medical Devices with Sharps Injury Prevention Features*; <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>.
 - b. Revise your proposed package insert to describe the revised product reconstitution and preparation process in a manner that clearly outlines each step. We strongly recommend the use of diagrams to enhance the directions for use.
3. The currently proposed product preparation process involves the use of an (b) (4) syringe. Depending upon your proposal in response to item 2 and 4 of this letter, reconfigure your product-powder vial label so that the product information can be transferred from the vial to the syringe or other appropriate system that will contain the final solution for administration into the bladder. This transferable label should contain, at a minimum, the product name, strength/milliliters and route of administration. Within the package insert's description of the product reconstitution process (see above), include this final step for affixing the transferable label to the syringe.

4. Your product's administration procedures are not adequately described within the proposed labeling. At the December 9, 2009 meeting, you demonstrated the procedures involved in injecting your product into the bladder. One procedural step involved the use of tubing labeled solely for the vascular administration of solutions; another procedural step involved the relatively rudimentary "plugging" of a Luer-tipped syringe (without the needle) and/or tubing into the non-conforming urine drainage tip of a bladder catheter. The use of tubing intended solely for intravascular use may increase the risk for vascular injection of your product. The lack of a properly designed connection between the delivery tubing or syringe may result in "spray" or "leakage" of the product and skin contact risks for both the patient and healthcare provider. To optimize the product administration procedures:
 - a. Redevelop the "kit" to contain a bladder catheter with a tip designed specifically to maintain a stable connection between the dilution-transfer system (item 1, above) and the bladder catheter. Alternatively, modify the proposed package insert to identify the specific bladder catheter(s) or catheter characteristics that must be used during the product's administration in order to maintain a stable syringe-bladder catheter connection. These connections must not rely upon manual pressure or necessitate manual manipulation to maintain the connection. Supply information that verifies the compatibility of your reconstituted product with the inner wall of the catheter, connecting tubing and adapter lumens.
 - b. Following administration of your product into the bladder, healthcare providers may apparently either remove the bladder catheter or maintain the catheter in place to prevent inadvertent early elimination of the product. Maintenance of the catheter within the bladder apparently must involve some form of catheter "clamping." Therefore, in addition to the bladder catheter features described above, the bladder catheter should allow for episodic clamping/occlusion.
 - c. Revise the proposed package insert to explicitly describe all the major steps involved in your product's administration into the bladder, including the procedures for connecting the Luer-tipped dilution/transfer system to the "in flow" bladder catheter tip. Include the use of diagrams/illustrations to add clarity to the sequential instructions. Explicitly describe whether the bladder catheter may be removed or whether it should remain in place for clamping/occlusion to prevent product elimination. Describe also how the product should be evacuated from the bladder following completion of the necessary retention time.

5. The cystoscopic examination procedure is insufficiently described within the proposed package insert. Certain aspects of your description of the examination procedures at the December 17, 2009 Advisory Committee Meeting appeared to refer to the “switching” between blue and white light during cystoscopy. Conceivably, this “switching” was intended to apply only to procedures performed followed completion of bladder mapping. A "switching" procedure has not previously been proposed as a component of your product's labeling. The lack of sufficient description of the cystoscopic examination procedure increases the risk for misdiagnosis or failed detection of cancer. To address these concerns:
 - a. Revise your proposed package insert to briefly describe the major steps involved in the cystoscopic examination procedure (as performed in the clinical trials) to ensure that all lesions identified by white light, blue light and both lights are appropriately mapped. If you wish to include procedures that involve “switching” between white and blue light, submit the appropriate documentation for consideration for possible inclusion in labeling. Consider the use of bladder maps or other figures/diagrams to enhance the informativeness of the description.
 - b. Proper use of your product involves thorough mapping of the bladder mucosa using white light followed by refinement of the mapping based upon the mucosal appearance with blue light illumination. Within your package insert revision, prominently describe the requisite bladder mapping procedures. Describe any video-mapping options or manual mapping procedures. As a component of labeling, consider the development of a unique procedural manual that, in addition to any other information, provides details of the cystoscopic examination techniques essential for safe and effective use of your product. This procedural document may expand upon summary information within the package insert. Insufficient description of the procedural steps within the package insert may necessitate the development of a unique procedural document as a component of labeling.
 - c. Supply a copy of a “Training Manual” that succinctly describes the use of your product and the essential aspects of cystoscopic examination using the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system. You may wish to combine this “Training Manual” with the procedural manual (cited above) to form a single document that comprises a component of the proposed labeling for your product.
 - d. In the development of your revised labeling, ensure consistency in the information contained between the labeling for your product and the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system.

6. Safety and efficacy data were supplied to support a single administration of your product. In the clinical trial (Study 305) submitted as confirmatory evidence of safety and efficacy, patients had to have a known or suspected bladder cancer, based upon findings from a prior cystoscopy.
 - a. Describe the proposed use of your product in urologic practice and incorporate important aspects of this description into the proposed labeling. Consider the following questions and requests:
 - i. Do you envision the use of your product among patients who have not previously undergone a cystoscopy?
 - ii. How should practitioners use your product if its use is limited to a single administration?
 - iii. Discuss recommendations to assist providers in identification of patients appropriate to receive your product, particularly considering its single use limitation.
 - b. We are particularly concerned about the potential for repetitive administrations of your product, despite labeling that describes its intended “single use.” Describe your plans for subsequent clinical studies that examine the safety and efficacy of repetitive administrations of your product. In general, we regard at least one adequate and well controlled study as essential to establish the safety and efficacy of repetitive product administrations.
7. Based upon our review of your response to the items listed above, additional clinical data may be necessary to assess the safety and efficacy of your product, including aspects related to product reconstitution and administration as well as the cystoscopic procedures.
8. Please be aware that any changes to the drug product formulation, container, closure or other drug contact surfaces (e.g., syringe, catheter, etc.) must be supported by the submission of correspondingly appropriate chemistry, manufacturing, and control (CMC) information and data (e.g., compatibility, stability, in-use testing, etc.). This consideration includes, but is not limited to, changes in the size and materials of construction and the addition of a co-packaged catheter.
9. Regarding our findings from the submitted clinical data, we note that Study 305 was submitted to confirm the safety and efficacy of your product. The desired statistical success was demonstrated for the “detection” co-primary endpoint but not for the “recurrence” co-primary endpoint. Post-hoc, exploratory analyses of the “supportive” studies showed “detection” findings generally consistent with those observed in Study 305. Study 304, the only supportive study that examined “recurrence,” failed to achieve its desired outcome.

- a. Together, these data generally indicate your product may assist in the detection of non-muscle invasive papillary bladder cancer. However, the data do not provide persuasive evidence that this detection results in a reduction of “recurrence.” This observation is based upon the failure to achieve statistical success for the “recurrence” outcomes as well as our inability to rule out uncontrolled bias in Study 305 associated with the open-label aspect of the follow-up period.
- b. Revise your proposed package insert (b) (4).

LABELING

10. Submit draft labeling that incorporates the requested revisions cited above. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

11. Submit draft carton and container labeling revised based upon the requested alterations, as listed above.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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If you have any questions, contact Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging
and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
12/30/2009

RAFEL D RIEVES
12/30/2009