CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

COMPLETE RESPONSE

Hope Pharmaceuticals
16416 North 92nd Street, Suite 125
Scottsdale, AZ 85260

Attention: Craig Sherman, M.D.
President

Dear Dr. Sherman:

Please refer to your New Drug Application (NDA) dated May 21, 2010, received May 21, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nithiodote (cyanide antidote kit containing co-packaged sodium nitrite injection and sodium thiosulfate injection).

We acknowledge receipt of your amendments dated June 16 and 25, July 2, 7, and 28, August 10, 17, 18, 20, 23, and 31(2), September 3, 8(2), 13, 17, 20, and 24, and October 15 and 22, 2010.

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

Deficiency: You have not provided adequate characterization of the (b) (4) leachate(s) in the drug products in order to conduct an adequate risk assessment for your product and justify your proposed product expiry. In order to resolve this deficiency you may consider the following options:

Option 1:

1. Establish the identity, source, and mass balance of the (b) (4) leachate(s). Reasonable approaches may include the methods reported through your primary literature searches (b) (4). A robust extractable study performed using the drug product solutions to extract all components of the container closure system will be required to address this deficiency.

2. Provide sufficient data to determine whether the leachable (b) (4) material will continue to increase on storage and what the anticipated exposure will be. Again, a robust extractable study performed using the drug product solutions to extract all components of the container closure system is required.

3. Provide an adequate toxicological risk assessment for the identified [redacted] (b) (4) leachable(s). This can be completed either via a new toxicology study or, if available, you may provide toxicology data from the literature to support the proposed exposure levels of the identified leachable(s), taking into consideration the route of administration. If definitive characterization of the [redacted] (b) (4) leachables is not possible and adequate intravenous toxicology data is not available in the literature, we recommend conducting a single-dose intravenous toxicology study in a single species that includes both acute and delayed observations (24 hours and 14 days), using drug product at the end of the proposed shelf-life. The dosing protocol should result in exposure to [redacted] (b) (4) compounds equal to or greater than that which will be administered to human via the use of drug product at the end of your proposed shelf life. The study should define a no adverse effect levels (NOAEL) or characterize acceptable toxicity for the proposed indication. Reference to comparable levels of exposure to a leachable via an FDA approved drug product(s) should be supported by actual data and appropriate 505(b)(2) patent certification.

Option 2:

4. Alternatively, you may propose a new container closure system that might have an acceptable leachable profile. Your search for a new container closure system might include, but should not be limited to, alternative rubber stoppers (e.g., [redacted] (b) (4)), different glass vial sources, and polypropylene bottles. With this option, a robust extractable study will be required, performed using the drug product solutions to extract all components of the container closure system. A minimum of six months of stability data (including leachables) using the new container closure system which includes results from testing at release, 3 months, and 6 months under real time storage and accelerated stability conditions will be required. Both conditions should include upright and inverted storage configurations. The extractable and leachable data from this new container system may be obtained from laboratory scale or pilot scale batches. Qualification or safety justifications will be required for leachable components from this new container closure system (refer to requirement #3 under Option 1).

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include 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.

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 other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RIGOBERTO A ROCA
11/18/2010