CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	January 14, 2011
From	Bob A. Rappaport, M.D.
Subject	Division Director Review and Summary Basis of Approval Action
NDA No.	201444
Applicant Name	Hope Pharmaceuticals
Date of Submission	December 22, 2010
PDUFA Goal Date	February 22, 2011
Proprietary Name / Established (USAN) Name	Nithiodote/ Sodium Nitrite 30 mg/mL and Sodium Thiosulfate 250 mg/mL
Dosage Forms / Strength	Solutions for injection/as above
Proposed Indication	Treatment of cyanide poisoning
Action	Approval

Material Reviewed/Consulted	
First Cycle Summary Review	Rigoberto Roca, M.D.
Pharmacology/Toxicology Review	Marcus Delatte, Ph.D. / R. Daniel Mellon, Ph.D.
CMC Review	Olen M. Stephens, Ph.D. / Xiaobin Shen, Ph.D./ Prasad Peri, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. / Suresh Doddapaneni, Ph.D.
ONDQA Biopharmaceutics Review	John Duan, Ph.D. / Patrick Marroum, Ph.D.
ONDQA Microbiology Review	Robert Mello, Ph.D. / John Metcalfe, Ph.D.
OSE/DMEPA	Denise V. Baugh, Pharm.D. / Todd Bridges, R.Ph. / Denise Toyer, Pharm.D. / Carol Holquist, R.Ph.
DDMAC	Mathilda Fienking

Cyanide poisoning is frequently lethal and, in addition to individual cases occurring due to accidents, exposure in fires or criminal activity, there is a high level of concern in the United States at this time that cyanide may be used against our troops in a war zone or in a terrorist attack, possibly by contamination of food. One of the long-standing treatments for cyanide poisoning has been the use of sodium nitrite and sodium thiosulfate, the latter administered immediately following the former. However, most of the marketed product was not FDA approved. The Agency has been attempting to provide approved product to the market for a number of years. Hope Pharmaceuticals originally submitted their application for Nithiodote on May 21, 2010. The review team concluded that they had provided adequate evidence of the safety and efficacy of Nithiodote, which primarily relied upon the referenced NDA for Hope's 505(b)(2) application. The referenced application, NDA 020166 submitted by the U.S. Army, only included a request to market sodium thiosulfate, as the Army had adequate supplies of sodium nitrite and only needed to procure new supplies of the sodium thiosulfate at the time that they submitted their application. However, the label for that product and nearly all of the supporting literature and medical information available clearly acknowledge that the thiosulfate is intended for administration immediately following sodium nitrite. As such, the Agency determined that a 505(b)(2) reference to NDA 020166 was essentially a reference to the two drug products used sequentially for the successful treatment of cyanide poisoning.

However, a Complete Response (CR) Letter was issued to the applicant on November 18, 2010. The CR action was taken because of an incompletely characterized impurity in the drug product. That impurity is a (b) (4) leachable(s), thought to be the result of the high pH of the solution acting on the glass container, possibly during (b) (4) sterilization (b) (4) (b) (4). Both the pharmacology/toxicology (P/T) and the CMC review teams recommended this action and Dr. Roca, our signatory for that action, concurred. Dr. Roca's review of the original submission, which summarizes all of the other reviews and available data, is attached to this review as an appendix, and my review will only address the single deficiency described below. The CR Letter listed the following requirements that would be necessary to address this concern:

> **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.
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> 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 (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 (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 (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., (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).

The applicant submitted their response to the CR letter on December 22, 2010. Upon review of that response and after extensive internal discussion, both the CMC and P/T review teams have determined that, while the impurity has still not been completely characterized, there is enough information available at this time to recommend approval with appropriate post-marketing studies required, particularly in light of the critically important nature of this product as a treatment for acute cyanide poisoning. One additional factor that was provided in the applicant's response and that was important in this decision was the determination that higher levels of (b) (4) leachables can be found in other FDA approved products and there are no clear safety signals associated with these impurities.

The following has been reproduced from page 7 of Dr. Stephens' review of the response to the CR Letter:

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, NDA 201-444 is recommended for approval.

Product quality concerns remain regarding (b) (4) leachable(s); however, in the judgment of the clinical division, this CMC deficiency should not prevent the approval of this NDA on the

basis of safety or efficacy deficiencies. Because this product is administered in life-threatening situations, the unknown risk of [redacted] (b) (4) leachable(s) is mitigated by the potential benefit of this antidote. Furthermore, the nonclinical review team is unaware of any safety signal associated with this class of impurity when administered intravenously. Without a clearly defined safety concern, product quality concerns were not sufficient to recommend a complete response by the clinical division. However, formal toxicology studies have not been performed to identify safety signals that may exist associated with [redacted] (b) (4) leachables, so the CMC deficiencies will be addressed through post-marketing requirements (see below) to further characterize the root cause of the leachables, its anticipated concentration, its rate of increase on storage, and potential strategies to minimize its concentration in the drug product solutions.

The CMC review team's recommendations for post-marketing requirements and commitments is summarized below, reproduced from pages 7 and 8 of Dr. Stephens' review:

B. Recommendation on Phase 4 (Post-Marketing) Requirements, Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Hope will provide the levels of [redacted] (b) (4) leachables from [redacted] (b) (4) testing (ideally from multiple batches) of an Agency-approved parenteral product(s) packaged in Type I USP [redacted] (b) (4)
2. Hope will report the results of an extractable study that individually investigates the rubber stopper and Type I USP [redacted] (b) (4) vial using both the drug product solutions (in independent experiments) as the extraction medium.
3. Hope will conduct pharmaceutical development studies to explore the possibility of using alternative container closure systems and [redacted] (b) (4) sterilization methods that might result in a more acceptable leachable profile. Robust extractable studies and stability data (including leachables) are required to support the manufacturing and packaging changes. Inverted (worst-case) storage configurations and stress conditions will be examined. Qualification or safety justifications will be required for leachables from these manufacturing changes.
   a. Alternative container closure systems may include alternative rubber stoppers (e.g., [redacted] (b) (4)), different glass vial sources, and polypropylene bottles.
   b. Alternative methods of [redacted] (b) (4) sterilization such as [redacted] (b) (4) [redacted] (b) (4) may be investigated. Any manufacturing changes will be validated in context of the expected microbial load.
4. Hope will amend the post-approval stability protocol to include leachable monitoring in the two drug products. The protocol will include monitoring at release, 3, and 6 months under accelerated stability conditions and monitoring at release, 6, 12, 24, 36, 48 and 60 months under real time storage conditions for the post-approval stability batches (at least the first three commercial batches).

The following has been reproduced from page 8 of Dr. Delatte's review of the applicant's response to the CR Letter:

1.3.1 Approvability

Technically, the sponsor has not provided adequate characterization of the toxicological effects of intravenous infusion of the [redacted] (b) (4) leachables detected in this drug product to conduct a toxicological risk assessment. However, they have provided information to suggest that individuals treated for [other serious, life-threatening conditions] with intravenous [FDA approved] products are apparently exposed to comparable levels of these leachables. Assuming the [redacted] (b) (4) leachables from [redacted] (b) (4) glass are of comparable chemical composition, given the potentially life-threatening indication and apparent lack of a safety signal from [these FDA

approved] injectable products, there does not appear to be a safety concern that would preclude approval of this product. However, as the Applicant's response is based on clinical experience with FDA approved drug products, the NDA may be approved at the discretion of the clinical review team.

1.3.2 Additional Nonclinical Recommendations

No nonclinical toxicology post marketing studies are recommended at this time, given the findings from the present application and the published literature, which suggest that drug products with a high pH may cause the leaching of (b) (4) chemicals from glass vials ((b) (4) (b) (4) These findings impact multiple products regulated by the Agency and therefore, if deemed necessary following further internal discussions, the Agency will consider means to address this issue across the products affected. The Pharmacology Reviewers have discussed this issue within the nonclinical pharmacology and toxicology hierarchy of the Agency.

From a nonclinical perspective, further studies may be recommended pending review of the results of the confirmatory post-marketing quality assessments requested by the chemistry, manufacturing, and controls (CMC) review team.

In Dr. Roca's review, he notes the fact that the referenced application (NDA 020166) was approved based only on animal data and, therefore, concludes that this application would need to be approved under Part 314.610, Subpart I of Title 21 of the CFR, commonly known as the Animal Rule. He goes on to state that approval under Subpart I would necessitate the applicant's completion of post-marketing clinical studies that captured safety and efficacy data from actual cases of cyanide poisonings treated with or without Nithiodote. However, NDA 020166 was not approved under the Animal Rule and no post-marketing studies were required for that approval. As this application was submitted under 505(b)(2) of the Food, Drug and Cosmetic Act, it cannot be held to a different standard than the referenced application. Therefore, no post-marketing clinical studies will be required for approval.

- Regulatory Action

  Approval

- Risk Benefit Assessment

  Cyanide poisoning is a frequently lethal event. It may occur in the setting of accidents, fires or criminal activity. Particularly concerning at this time is the potential for cyanide to be used in mass poisonings of military personnel in war zones or the civilian population in a terrorist attack. It is essential that adequate supplies of FDA approved treatments are available for intervention, particularly in the latter scenarios. While the applicant has not completely characterized the (b) (4) leachable(s) in their product, it would not be acceptable to hold up approval of Nithiodote any longer to allow them to complete that characterization. We are fortunate that the applicant was able to supply additional information in their response to the CR letter, particularly those data regarding already FDA-approved products that contain similar quantities of (b) (4) leachable(s). This information lowers our concern about the potential

toxicity of the impurity in their product. We will require full characterization of the impurity in the immediate post-marketing period and the applicant has agreed to complete that work as quickly as possible.

- Post-Marketing Requirements (PMR)

  - A non-clinical study to assess the levels of (b) (4) leachables (in triplicate) from multiple batches of an agreed upon Agency-approved parenteral product(s) packaged in Type I USP (b) (4)

  - An extractable study that individually investigates the rubber stopper and Type I USP (b) (4) vial using both the drug product solutions (in independent experiments) as the extraction medium

- Post-Marketing Commitments (PMC)

  - Evaluate alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile.

  - Amend the post-approval stability protocol to adequately monitor (b) (4) leachable material.

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/s/

BOB A RAPPAPORT
01/14/2011