CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203922Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 14, 2012
From	Arthur Simone, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203922
Applicant	Hope Pharmaceuticals
Date of Submission	January 10, 2012
PDUFA Goal Date	November 10, 2012
Proprietary Name / Established (USAN) names	Not Applicable / Sodium Nitrite
Dosage forms / Strength	Solution, Injection / 30 mg/mL
Proposed Indication(s)	Treatment of life-threatening cyanide poisoning
Recommended:	Approval

Reference ID: 3087585

1. Introduction

On January 14, 2011, the Applicant, Hope Pharmaceuticals, received approval for Nithiodote (NDA 201444), a combination product consisting of sodium thiosulfate and sodium nitrite for the treatment of acute cyanide poisoning that is judged to be life-threatening. To allow product users, e.g., the military and hospitals, to maintain their supply of product without having to replace the entire combination package when only one component has reached expiry, the Applicant now submits a separate 505(b)(2) application for each of the components, sodium thiosulfate and sodium nitrite, for the same indication but with labeling that reflects the need to use both products sequentially.

This review contains summaries of the regulatory interactions between the Applicant and the Agency relevant to this NDA, outstanding issues related to Nithiodote that are applicable to sodium nitrite, a review of the proposed labeling, and recommendations for regulatory action. The reader is referred to the primary and secondary review by the individual disciplines for the Nithiodote NDA for detailed information regarding each of the components as well as the appropriate method of administration to treat cyanide poisoning.

2. Background

A teleconference was held between the Agency and the Applicant on December 16, 2011, to discuss what would be required to file an NDA for the individual components of Nithiodote. The following items were agreed upon during that teleconference:

- Each component requires its own NDA if it is to be packaged and marketed separately from Nithiodote.
- The NDAs for the individual components of Nithiodote may cross-reference the Nithiodote NDA (NDA 201444) for
  - Module 2, Common Technical Document Summaries
  - Module 3, Quality
  - Module 4, Nonclinical Study Reports
  - Module 5, Clinical Study Reports
- Container labeling and package inserts for the individual component products have to reflect the need to use both the sodium nitrite and the sodium thiosulfate in sequential fashion to treat cyanide poisoning.

On January 10, 2012, the Applicant submitted to NDA 201444 a letter of authorization allowing the Nithiodote NDA to be cross referenced by NDA 203923 for sodium thiosulfate injection and NDA 203922 for sodium nitrite injection.

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3. CMC/Device

In the Approval letter for Nithiodote (NDA 201444), several CMC-related items were included as postmarketing requirements (PMR) and commitments (PMC). All but one of these, a PMC, has been fulfilled by the Applicant. The remaining PMC is applicable to Sodium Nitrite Injection when marketed alone. At the time of this review, this PMC has not been fulfilled or released and, therefore, should be included in the Approval letter for this NDA. Drs. Xiaobin Shen and Prasad Peri, who performed the CMC review for this NDA, concur with this recommendation in their review. Specifically, the following PMC wording should be incorporated into the Approval letter:

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

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

On February 9, 2012, the Applicant proposed to conduct an appropriate study to fulfill this PMC according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	07/2012
Final Report Submission:	08/2012

This schedule is acceptable. As this is the same PMC as issued for NDA 201444 Nithiodote (sodium nitrite and sodium thiosulfate) at the time of its approval in 2011, the same study should be allowed to fulfill the postmarketing commitment for this NDA as well.

The completed CMC review also states the following:

1. The facilities involved in the manufacturing and testing of the drug substance and drug product are the same as those for NDA 201444, and that the Office of Compliance has reported an overall acceptable recommendation for all facilities on January 30, 2012.
2. Sufficient stability data have been submitted, in Supplement 3 to NDA 201444 (dated October 25, 2011; SDN 42; eCTD Sequence Number 038), to warrant a 24-month expiry.
3. The product labeling (i.e., package insert and container labeling) is acceptable.
4. A categorical exclusion has been granted for the Environmental Assessment/Claim of Categorical Exclusion.

The CMC team recommends an approval action be taken with the single PMC listed above included in the Approval letter.

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4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology and toxicology issues related to sodium nitrite have been addressed by the referenced NDA (Nithiodote; NDA 201444).

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology and biopharmaceutics issues related to sodium nitrite have been addressed by the referenced NDA (Nithiodote; NDA 201444).

6. Clinical Microbiology

Not Applicable. Sodium nitrite is not a therapeutic antimicrobial.

7. Clinical/Statistical - Efficacy

Clinical efficacy and statistical issues related to sodium nitrite have been addressed by the referenced NDA (Nithiodote; NDA 201444).

8. Safety

Safety issues related to sodium nitrite have been addressed by the referenced NDA (Nithiodote; NDA 201444).

9. Advisory Committee Meeting

Input from the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) was not required for the approval of Nithiodote. There were no issues for this NDA that required a convening of the AADPAC.

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10. Pediatrics

The Applicant has received orphan drug designation for sodium nitrite for the treatment of known or suspected cyanide poisoning, and is, therefore, not subject to the requirements under the Pediatric Research Equity Act (PREA).

Pediatric dosing information contained in the Nithiodote label has been appropriately included in the label for sodium nitrite.

11. Other Relevant Regulatory Issues

By agreement with the Agency, this NDA consists of CMC and labeling information only. As indicated in the sections above, the Nithiodote NDA (201444), held by Hope Pharmaceuticals, was referenced for the necessary nonclinical, clinical pharmacological and clinical information for an NDA submission. There were no issues related to exclusivity or patent certification, and there was no need for financial disclosures or Division of Scientific Investigation involvement. During the review process, no new regulatory issues were raised.

12. Labeling

As described above, the package insert and container labeling were to reflect the indication of this product, i.e., to treat cyanide poisoning, and the need to use it sequentially with sodium thiosulfate. In discussions between the Division and the Applicant, it was agreed that the package insert for Nithiodote could be modified to be used as the package insert for each of the components when marketed individually.

The package insert and the container and carton labels were reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). Their recommendations were passed on to the Applicant who made the required changes. On their review of the amended label, the DMEPA team concluded that all the labeling was acceptable. I concur with their conclusion.

A copy of the updated package insert, immediate container label and carton label can be found in the Appendix below.

As was the case for Nithiodote, the Patient Counseling Information section of the package insert was limited due to the likelihood that patients would be unconscious or unresponsive at the time sodium nitrite would be administered. For the same reason, a medication guide was not deemed necessary.

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13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
It is recommended that this NDA be approved for the proposed indication and with the proposed package insert and carton labeling.

Benefit Risk Assessment
With the approval of Nithiodote, the Agency found that the benefits outweighed the risks for the sequential use of sodium nitrite and sodium thiosulfate, when each is manufactured by the methods and in the facilities used by Hope Pharmaceuticals. There is no evidence to suggest that the benefit or risk would be altered by the marketing of the components of Nithiodote individually for the same indication. Allowing the individual components, i.e., sodium nitrite and sodium thiosulfate, to be marketed individually for the purpose of replacing expiring product in the Nithiodote package may provide additional benefits including:

- Reduced cost to consumers, as replacing the individual components will likely be less expensive than replacing the combination product, i.e., Nithiodote.
- Reduced waste, as unexpired components will not have to be discarded.
- Potentially less impact on public safety if issues arise that limit the availability of either Nithiodote or the marketed individual components, as residual supplies of one could compensate, to a degree, for the lack of the other.

There were no differences of opinion among members of the review team as to whether this NDA should be approved or whether the marketing of this component of Nithiodote by itself adversely affects the benefit or risk profile observed for Nithiodote.

Recommendation for Postmarketing Requirements and Commitments
The remaining unfulfilled postmarketing commitment that was made by the Agency as part of the approval of Nithiodote, and which is to sodium nitrite, should be included with the approval of this NDA as it is relevant to sodium nitrite when packaged alone for the proposed indication. Specifically, the following PMC, worded as it was in the Approval Letter for NDA 201444 but with a new PMC number, should be included in the Approval letter:

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

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

Recommendation for Postmarketing Risk Evaluation and Management Strategies
The approval of Nithiodote did not require either restricted distribution of the product or any component of a Postmarketing Risk Evaluation and Management Strategies (REMS). There is nothing unique about the individual components of Nithiodote, sodium nitrite in

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particular, that would warrant these restrictions or postmarketing activities for the proposed indication.

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APPENDIX

Labeling – Package Insert

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

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02/14/2012

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02/14/2012