CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203922Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	February 14, 2012
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA / Supplement #	NDA 203922
Applicant Name	Hope Pharmaceuticals
Date of Submission	January 10, 2012
PDUFA Goal Date	November 10, 2012
Proprietary Name / Established (USAN) Name	Not Applicable / sodium nitrite
Dosage Forms / Strength	Solution for injection / 30 mg/mL
Proposed Indication(s)	Treatment of life-threatening cyanide poisoning
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Arthur Simone, M.D., Ph.D.
Statistical Review	Not applicable
Pharmacology Toxicology Review	Not applicable
CMC Review	Xiaobin Shen, Ph.D. / Prasad Peri, Ph.D.
Microbiology Review	Not applicable
Clinical Pharmacology Review	Not applicable
DSI	Not applicable
OSE/DMEPA	Denise V. Baugh, Pharm.D. / Lubna Merchant, Pharm.D. Carol Holquist, R.Ph.

CDTL = Cross-Discipline Team Leader
DMEPA = Division of Medication Error Prevention and Analysis
DSI = Division of Scientific Investigations
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Hope Pharmaceuticals, received approval to market Nithiodote, a combination product consisting of sodium thiosulfate and sodium nitrite, for the treatment of acute cyanide poisoning that is judged to be life threatening on January 14, 2011 (NDA 201444). That application was a 505(b)(2) application, referencing NDA 020166 held by the Department of the Army, Office of the Surgeon General. The Army requested withdrawal of NDA 020166 on March 24, 2004; the Division is not aware of any data to suggest that the product is unsafe or ineffective.

The Applicant has submitted 505(b)(2) applications for each of the components for the same indication, with the product labeling reflecting that the both products are to be used sequentially; NDA 203922 is for the sodium nitrite, and NDA 203923 is for the sodium thiosulfate.

This review will provide an overview of the regulatory and scientific facts of this supplemental application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling modifications requested by the Applicant.

2. Background

The NDA for Nithiodote (NDA 201444) only permits the marketing of the two drug products, sodium nitrite and sodium thiosulfate, as components of one package. Since the drug products have different expiry dates, this has necessitated that product users, such as the military and hospitals, replace the entire package when only one of the components has reached its expiry date. By submitting separate applications for the two products, the Applicant intends to market the components separately, thus increasing the flexibility for product users as they manage their supply stocks.

In discussions with the Division, it was agreed that the Applicant could submit new 505(b)(2) applications for the individual components which could, by reference, rely on the information contained in the NDA for Nithiodote. Specifically, the new NDAs for the individual components would be able to reference NDA 201444 for the following data and information:

- Module 2, Common Technical Document Summaries
- Module 3, Quality
- Module 4, Nonclinical Study Reports
- Module 5, Clinical Study Reports

It was also noted during the discussions with the Applicant that the container labeling and package inserts for the two NDAs would need to reflect the need to use both products in a sequential manner in order to treat cyanide poisoning.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

There was no new CMC information submitted; all supporting information and data for this NDA was on the basis of reference to NDA 201444 and was, therefore, deemed acceptable.

Facilities Review/Inspections

The Office of Compliance has found them acceptable.

Outstanding or Unresolved Issues

In the approval letter for Nithiodote, NDA 201444, two post-marketing requirements and two post-marketing commitments were noted for the sodium nitrite component of the NDA. They were the following:

Post-marketing requirements

- 1726-1 A non-clinical study to assess the levels of (b) (4) leachables (b) (4) from multiple batches of an agreed upon Agency-approved parenteral product(s) packaged in Type I USP (b) (4)

- 1726-2 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

- 1726-3 Evaluate alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile

- 1726-4 Amend the post-approval stability protocol to adequately monitor (b) (4) leachable material

Of the above, the applicant fulfilled the two post-marketing requirements, and submitted information to address the second post-marketing commitment. As the first post-marketing commitment, Commitment 1726-3, is relevant to a situation where the sodium nitrite is marketed individually, it will be included in the letter for this NDA. When the Applicant addresses this commitment for one NDA, it will also address it for the other.

The review team reviewed the stability data submitted by the Applicant to NDA 201444 (Supplement 3, SDN 42, received on October 25, 2011). The data in the supplement supports an expiry of 24 months for the sodium nitrite, when stored at controlled room temperature between 20º C and 25º C (68º F to 77º F), with excursions permitted to 15º C to 30º C (59º F to 86º F).

4. Nonclinical Pharmacology/Toxicology

There was no nonclinical information required or submitted with this application. As noted by Dr. Simone, nonclinical pharmacology and toxicology issues related to sodium nitrite have been adequately addressed in the referenced NDA for Nithiodote (NDA 201444).

5. Clinical Pharmacology/Biopharmaceutics

There was no clinical pharmacology or biopharmaceutics information required or submitted with this application. As noted by Dr. Simone, clinical pharmacology and biopharmaceutics issues related to sodium nitrite have been adequately addressed in the referenced NDA for Nithiodote (NDA 201444).

6. Clinical Microbiology

Sodium nitrite is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

There was no clinical efficacy data required or submitted with this application.

8. Safety

There was no safety data required or submitted with this application.

9. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Division of Scientific Investigations (DSI) Audits

The Division of Scientific Investigations (DSI) was not consulted to conduct any clinical site inspections, as there were no clinical studies conducted in support of this NDA.

Financial Disclosure
There were no clinical studies conducted in support of this NDA.

Consult from Division of Medication Error Prevention and Analysis
The Division of Medication Error Prevention and Analysis identified several aspects of the proposed package insert and container label that could contribute to medication errors. Their observation and recommendations were conveyed to the Applicant, and the subsequent modifications were deemed acceptable.

Outstanding or Unresolved Issues
There are no other unresolved relevant regulatory issues.

12. Labeling

As noted by Dr. Simone, the package insert and container labeling for this NDA was to reflect the indication of this product, i.e., treatment of cyanide poisoning, and to note that it needed to be used sequentially with sodium thiosulfate. Modification of the package insert and container labeling of Nithiodote by the Applicant was an acceptable strategy, which was conveyed to the Applicant in discussions prior to the submission of this NDA.

As noted above, representatives from the Office of Surveillance and Epidemiology were consulted and their recommendations were incorporated during the discussion of the label.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

The risk:benefit assessment of Nithiodote was previously deemed to have been acceptable; there is no reason to interpret that the marketing of the individual components of Nithiodote would alter that assessment. In fact, as noted by Dr. Simone, there is the possibility that having the individual components available to be marketed separately may provide additional benefits, such as reduced cost (replacement of individual components will likely cost less than replacement of Nithiodote), and reduced waste (unexpired components in the Nithiodote product would not need to be discarded).

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Commitments

The remaining outstanding commitment from NDA 201444 is also applicable to this NDA and should therefore be included:

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

When the Applicant addresses this commitment for one NDA, it will also address the commitment for the other NDA.

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/s/

RIGOBERTO A ROCA
02/14/2012