CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

MEDICAL REVIEW(S)

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

Summary Review for Regulatory Action

Date	November 18, 2010
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA No.	201444
Applicant Name	Hope Pharmaceuticals
Date of Submission	May 21, 2010
PDUFA Goal Date	November 19, 2010
Proprietary Name / Established (USAN) Name	Nithiodote (Sodium Nitrite and Sodium Thiosulfate) Injection
Dosage Forms / Strength	Injection - Sodium nitrite 300 mg (30 mg/mL) and Sodium thiosulfate 12.5 g (250 mg/mL)
Proposed Indication	Treatment of cyanide poisoning
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer 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 Fienkeng, Pharm.D.

CDTL = Cross-Discipline Team Leader
DDMAC = Division of Drug Marketing, Advertising and Communication
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, has submitted a 505(b)(2) application for their product Nithiodote, consisting of sodium nitrite and sodium thiosulfate, for the treatment of known or suspected cyanide poisoning. The Applicant is relying on the Agency's finding of safety and effectiveness for a previously approved application, NDA 020166. The referenced NDA was for the sodium thiosulfate component; however, the data in support of that NDA indicated that the product was only shown to be effective when used concomitantly with sodium nitrite. Based on this assessment, the Agency has concluded that there was a prior finding of safety and effectiveness for the two components, and this application may rely upon that finding.

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

Sodium nitrite and sodium thiosulfate have been marketed in the United States for almost 80 years. A two-component kit (sodium nitrite and sodium thiosulfate) and a three-component kit (sodium nitrite, sodium thiosulfate, and amyl nitrite) for the treatment of cyanide poisoning have been unapproved products marketed in the United States since before 1962.

In 1991, the United States Army submitted an application for sodium thiosulfate, NDA 020166. The application was only for sodium thiosulfate because the Army had adequate supplies of sodium nitrite and needed only to procure new supplies of the sodium thiosulfate. However, the intent for the sodium thiosulfate in the application was for it to be used in conjunction with sodium nitrite; the application was approved in February 1992.

An internal review of the documents supporting the approval package for NDA 020166, as well as a review of the literature available from the time of the application to 2007, resulted in the determination that the approval of sodium thiosulfate was actually an approval for the concomitant use of sodium thiosulfate and sodium nitrite.

This determination was conveyed to the Applicant at a pre-IND industry meeting held in July 2007. The meeting minutes from that meeting indicate that the Applicant was informed that applications for the administration of the two components, sodium nitrite and sodium thiosulfate, in a manner consistent with the approved label for NDA 020166, would not be required to submit additional toxicological, pharmacokinetic, or clinical information to support the safety or efficacy of the two products. The approval of the application would depend on the adequacy of the chemistry, manufacturing, and controls (CMC) information, and the related inspections.

It is important to note that the data supporting NDA 020166 was a review of the literature that included articles in support of efficacy only on use in animals, as controlled clinical trials were not feasible.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The product, Nithiodote, consists of one 10-mL vial of sodium nitrite (30 mg/mL; 300 mg of sodium nitrite) and one 50-mL vial of sodium thiosulfate (250 mg/mL; 12.5 grams of sodium thiosulfate).

The review team's assessment of the data supporting the drug substances was that it was adequate to support approval. However, the data supporting the drug product identified very limited stability data (6 months long term and accelerated data), and (b) (4) leachables. Preliminary investigations by the Applicant appear to indicate that the leachables are from the container closure system, which seems plausible as the pH of the formulation and method of sterility have the potential for leaching (b) (4) compounds from the glass container and/or rubber stopper.

However, the Applicant was not able to provide data that conclusively identified the source or the identity of the (b) (4) leachables; therefore, it is not possible for the review team to complete a safety evaluation of the leachables in the drug product at this time.

Facilities Review/Inspections

The Office of Compliance completed the manufacturing facilities site inspections and issued an overall recommendation of acceptable on September 21, 2010.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance; the application cannot be approved at this time.

4. Nonclinical Pharmacology/Toxicology

As noted above, the Applicant had been informed that additional toxicological data did not need to be submitted with the application. However, that conclusion was predicated on the assumption that formulation-specific issues would not be identified. As noted in Section 3, the CMC data identified (b) (4) compounds in the leachate, as well as evidence that there were increasing levels of (b) (4) compounds over time. As the Applicant has not provided adequate data to permit a definitive toxicological risk assessment for the levels of leachable (b) (4) compounds from the container closure system to support the expiry time period proposed in the application, the review team has recommended that the application not be approved.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Delatte and Mellon that, in order for this application to be approved, the Applicant must submit definitive intravenous toxicology data from nonclinical studies to support the safety of the levels of (b) (4) compounds present in the drug product. Alternatively, if the chemical composition of the (b) (4)

(b) (4) impurities can be identified, the Applicant may be able to provide toxicology data from the literature to support the proposed exposure levels.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval, other than agreement on the product label.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The effectiveness of the two-component regimen is based on sodium thiosulfate's ability to function as a sulfur ion donor, allowing the enzyme rhodanase to convert cyanide to the nontoxic thiocyanate. Because this conversion is a slow process, respiratory support and the administration of sodium nitrite, with its ability to induce the formation of methemoglobin which then binds to the cyanide ion to form cyanomethemoglobin, are critical to allow additional time for the sodium thiosulfate and rhodanase to reduce the cyanide load.

It is not possible to conduct clinical trials for this indication. The Applicant is relying on the Agency's finding of efficacy for NDA 020166, which, in turn, relied on literature, including evidence of efficacy from animal studies.

8. Safety

The Applicant is relying on the Agency's prior finding for NDA 020166 to support the safety of the sodium nitrite and sodium thiosulfate components; no additional data in support of either component were submitted in support of the application. The Applicant did submit a review of the adverse events reported in the literature and adverse events reported for the marketed products as part of the 120-day safety update. No new safety signals were identified.

9. Advisory Committee Meeting

It will not be necessary to present this application before an advisory committee. The available efficacy and safety data permits a favorable risk-benefit analysis that provides a strong support for approval of the application, once the CMC and the nonclinical deficiencies have been adequately addressed.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Division of Scientific Investigations 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 the Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications provided several comments regarding the package insert, and the carton and container labeling. The comments were incorporated as appropriate during the course of the review of the proposed label.

Consult from the Division of Medication Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the label. The comments were incorporated as appropriate during the course of the review of the proposed label. A proprietary name review was also conducted by the DMEPA, and they found the name Nithiodote acceptable.

Post-marketing Requirements Based on the Regulatory Basis of Approval

This product would be approved under Part 314.610, Subpart I of Title 21 of the Code of Federal Regulations (CFR). Applications approved under this regulation are subject to three requirements: 1) postmarketing studies, 2) approval with restrictions to ensure safe use, and 3) information to be provided to patient recipients.

1. *Post-marketing studies*

The CFR stipulates that the Applicant must "…conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical." Further, Applicants must "…include as part of their application, a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible."

It is believed that it is both ethical and feasible for the Applicant to monitor the use of this product post-approval; therefore, a post-marketing commitment should be made and a proposed plan submitted to gather safety and efficacy data during initial marketing. Specific questions that should be addressed include an assessment of the adequacy of the dosing regimen and the need for dose adjustments in certain patient populations.

2. *Approval with restrictions to ensure safe use*

The CFR stipulates that "…if FDA concludes that a drug product shown to be effective under this regulation can be safely used only if distribution or use is restricted, FDA will

require such postmarketing restrictions as are needed to ensure safe use of the drug product,…" and the restrictions will be commensurate with the specific safety concerns presented by the drug product. The examples noted in the CFR are:

(a) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(b) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(c) Distribution conditioned on specified recordkeeping requirements.

Since the nature of the indication for this product requires that it be widely and readily available in places such as hospital emergency departments, ambulances and fire-rescue units, it is believed that further restrictions would be inappropriate.

3. *Information to be provided to patient recipients*

The CFR stipulates that, for drug products or specific indications approved under this regulation, the Applicant must "…prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the drug product for the use approved under this regulation, if possible."

Although it is possible and appropriate for the labeling to contain the information indicated in the CFR, the clinical scenarios in which treatments for cyanide poisoning will be used will generally not permit an opportunity for the patient to review the labeling prior to administration of the product. Therefore, the part of the requirement that stipulates that the patient labeling must be available with the product in order to be provided to the patient prior to administration or dispensing of the product will be waived.

12. Labeling

The review team has reviewed the label proposed by the Applicant and has made substantial revisions. A final label will require further discussions with the Applicant; since it will not be possible to approve the application at this time, these discussions will be undertaken during the subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

I concur with the review team that, while there is evidence that this product will be safe and effective once appropriate labeling has been agreed upon, and if that

labeling is attended to by the prescribers, the current drug product quality deficiencies preclude approval of the application at this time.

It was noted during the review of the application that the data for the product would only support a 6-month expiry, and the available product had already exceeded the expiry time point, if, in fact, a shelf-life were to be designated by the review team. Further, the Applicant is not actively manufacturing more product, and a manufacturing facility is not expected to come online until some time during the first quarter of 2011. However, none of these findings are viewed as deficiencies from the standpoint of approvability of the NDA, and did not come into consideration in the paradigm for the decision as to whether the application could be approved or not. The application had a specific deficiency identified, as noted above, which precluded approval; once data are submitted to address that deficiency, and agreement is reached with the Applicant on the labeling and package insert, I expect that the application will likely be approved.

Recommendation for Postmarketing Risk Management Activities

Under 21 CFR 314.610, the Applicant is required to provide restrictions to ensure safe use of their product if the Agency determines that it can only be use safely with restricted use. Due to the fact that the product will need to be widely distributed, restrictions on use would be inappropriate.

Recommendation for other Postmarketing Study Commitments

The Applicant will be required to submit a proposed plan to gather safety and efficacy data from field studies during initial marketing. Specifically, the adequacy of the dosing regimen will need to be assessed and the need for dose adjustments in certain patient populations will need to be evaluated.

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/s/

RIGOBERTO A ROCA
11/18/2010