

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

201444Orig1s000

Trade Name: Nithiodote

Generic Name: Sodium Nitrite; Sodium Thiosulfate

Sponsor: Hope Pharmaceuticals

Approval Date: 1/14/11

Indications: Indicated for the treatment of acute cyanide poisoning that is judged to be life-threatening.

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

NDA APPROVAL

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 (FDCA) for Nithiodote (sodium nitrite injection USP and sodium thiosulfate injection USP for intravenous infusion).

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, October 15 and 22, November 19, December 6 and 22, 2010, and January 12, 2011.

The December 22, 2010, submission constituted a complete response to our November 18, 2010, action letter.

This new drug application provides for the use of Nithiodote (sodium nitrite injection USP and sodium thiosulfate injection USP) for sequential use for the treatment of acute cyanide poisoning that is judged to be life-threatening.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 201444.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Nithiodote is a cyanide antidote drug for which there are no approved comparable products. It is intended for a potentially life-threatening exposure to cyanide. The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been fully characterized or qualified but appears to increase with time on storage. Although there is no safety signal known for this class of impurity when administered intravenously, no toxicology studies have been performed to establish a No Adverse Effect Level (NOAEL). Given that the toxicological profile has not been adequately characterized in terms of risk, exposure to this (b) (4) leachable may have a potential to result in serious adverse effects following intravenous administration of Nithiodote.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk that may be associated with exposure to the (b) (4) leachable described above.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

- 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)

The timetable you submitted on January 12, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2011
Study Completion: 05/2011
Final Report Submission: 06/2011

- 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

The timetable you submitted on January 12, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2011
Study Completion: 05/2011
Final Report Submission: 06/2011

Submit the protocols to your PIND 078597 file, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

“Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any post-marketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments:

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

The timetable you submitted on January 12, 2011, states that you will conduct this study according to the following schedule:

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

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

The timetable you submitted on January 12, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2011
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Submit clinical protocols to your PIND 078597 file for this product. Submit nonclinical and chemistry, manufacturing, and controls (CMC) protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

EXPIRATION DATE

A shelf-life of 12-months is granted for each drug product found in NITHIODOTE®. The expiry for NITHIODOTE® is limited to the component with the shortest shelf-life remaining.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling