

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203922Orig1s000

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Memorandum

To: NDA 203-922

Subject: To amend the NDA with the updated product expiry of 24 months.

From: Xiaobin Shen, Ph.D., Reviewer, Branch VIII, Division III, ONDQA.

NDA 203-922 referenced to NDA 201-444 for support of CMC information.

Supplement-003 of NDA 201-444 has been reviewed and an expiry of 24 month is granted for the sodium nitrite product.

Hence, this memorandum updates the expiry of sodium nitrite in NDA 203-922 from the previously granted (b) (4) months.

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/s/

XIAOBIN SHEN

02/14/2012

Updated expiry to 24 months.

ERIC P DUFFY

02/14/2012

NDA 203-922

Sodium Nitrite, 30 mg/mL

Hope Pharmaceuticals

Xiaobin Shen, Ph.D.
Division of Anesthesia, Analgesia and Addiction Drug
Products

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Chemistry Review Data Sheet

1. NDA 203-922
2. REVIEW #: 1
3. REVIEW DATE: 31-Jan-2012
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

03-Jan-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Hope Pharmaceuticals

Address: 16416 N. 92nd Street #125
Scottsdale, AZ 85260

Representative: Craig Sherman, M.D.

Telephone: 480-607-1970

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sodium Nitrite Injection, USP

b) Non-Proprietary Name (USAN): Sodium Nitrite

Chemistry Review Data Sheet

- c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1S
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(2)

10. PHARMACOL. CATEGORY: Antidote

11. DOSAGE FORM: IV Injection

12. STRENGTH/POTENCY: Sodium Nitrite, 30 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

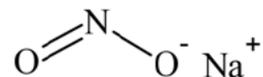
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sodium Nitrite

Chemical name, USAN, and Compendial Name: Sodium Nitrite

Chemical structure:



Molecular formula: NaNO_2

Molecular weight: 69.0 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3*	Adequate	14-Oct-2008	Reviewed by Dr. Donald Klein
	V			7	Adequate	05-Jan-2009	Reviewed by Dr. Steven Donald
	III			7	Adequate	NA	(b) (4) meets safety requirement per MAPP (b) (4)

* The stopper used in this NDA is (b) (4) reviewed previously and deemed adequate to support various injection products. The most recent review was performed by Dr. Donald Klein on 14-Oct-2008. The stopper (b) (4) reviewed by Dr. Mark Sassaman on 12-Apr-2007 and deemed adequate. The DMF was reorganized and resubmitted on 08-May-2009 with information related to other coating materials.

- ¹ Action codes for DMF Table:
 1 – DMF Reviewed.
 Other codes indicate why the DMF was not reviewed, as follows:
 2 –Type 1 DMF
 3 – Reviewed previously and no revision since last review
 4 – Sufficient information in application
 5 – Authority to reference not granted
 6 – DMF not available
 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	All are referenced to the already approved NDA 201-444, no further assessment is required. See details in the Executive Summary.		
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DMEPA/OSE			
EA			
Microbiology			

The Chemistry Review for NDA 203-922

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

This NDA is submitted for the purpose of having individually packaged sodium nitrite component of the Nithiodote drug product already approved in NDA 201-444. There is no further change beyond those related to package insert, packaging carton and carton labeling.

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

Not applicable for this NDA. All relevant information is referenced to NDA 201-444.

At the time of approval for NDA 201-444, the following Post Marketing Requirements (1 & 2) and Post Marketing Commitments (3 & 4) were established —

1. Hope will provide the levels of (b) (4) leachables (b) (4) testing (ideally from multiple batches) of an Agency-approved parenteral product(s) packaged in Type I USP (b) (4)
2. Hope will report the results of 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.
3. Hope will conduct pharmaceutical development studies to explore —
 - a. Alternative container closure systems that may include alternative rubber stoppers (b) (4) different glass vial sources, and (b) (4) bottles.
 - b. Alternative methods of (b) (4) sterilization (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).

Items 1 and 2 (PMRs) were satisfied on 22-Mar-2011, for details refer to the CMC Memo to File conducted by Dr. Olen Stephens on 30-Mar-2011.

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Item 4 (PMC) was satisfied on 23-Feb-2011, for details refer to the CMC Memo to File conducted by Dr. Olen Stephens on 01-Mar-2011.

Hence, for the referenced NDA 201-444, only one PMC (Item 3) is outstanding.

II. Summary of Chemistry Assessments

All CMC information is referenced to NDA 201-444. Only brief summary information is provided below. cGMP status of all facilities are acceptable.

A. Description of the Drug Substance and Drug Product

The sodium nitrite drug substance is manufactured under cGMP from a food grade sodium nitrite source that complies with Food Chemicals Codex (FCC). The sodium nitrite is (b) (4). The sodium nitrite drug substance is (b) (4). Sufficient stability data is provided to grant a (b) (4) retest date for the sodium nitrite drug substance.

NDA 203-922 is submitted as a 505(b)(2), based on the approved NDA 201-444, NITHIODOTE® Injection. The sodium nitrite injection product is indicated for, and used in combination with sodium thiosulfate injection, the treatment of acute cyanide poisoning that is judged to be life-threatening. The sodium nitrite injection product is individually packaged, in contrast to that co-packaged with sodium thiosulfate in NDA 201-444. The package insert and carton labeling are modified to reflect this package configuration.

The sodium nitrite drug products is formulated as a solution followed by (b) (4) sterilization (b) (4). The sodium nitrite drug product is a simple solution dissolved in WFI. It is filled into USP Type 1 (b) (4) glass vials and stoppered (b) (4) stoppers and a (b) (4) aluminum overseal. The vials are packaged in a (b) (4) box, the secondary container. Release and stability testing include testing for bacterial endotoxins, sterility, and container integrity testing. Photostability, thermostability, oxygen stress, and temperature cycling studies showed the drug product as insensitive to these stability stressors. Sufficient stability data is provided to allow a (b) (4) month shelf life.

B. Description of How the Drug Product is Intended to be Used

The following dosing regimen is proposed. Sodium nitrite is administered first followed immediately by sodium thiosulfate. The same needle and vein may be used to administer both solutions.

Adults:

Sodium Nitrite: 10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute.

Executive Summary Section

Sodium Thiosulfate: 12.5 g (50 mL of a 25% solution) immediately following administration of sodium nitrite.

Redosing: If a patient does not respond to initial doses, treatment may be repeated with one-half the original dose of sodium nitrite followed by one-half the original dose of sodium thiosulfate.

Children:

Sodium Nitrite: 0.2 mL/kg of a 3% solution (6 mg/kg or 6-8 mL/m² BSA) of sodium nitrite at the rate of 2.5 to 5 mL/minute not to exceed 10 mL (300 mg).

Sodium Thiosulfate: 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30-40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose.

Storage and Expiry:

Store between 20°C and 25°C (68°F - 77°F); excursions permitted to 15 - 30°C (59°F - 86°F). Protect from direct light and keep the vials in their secondary container. Do not permit the drug products to freeze. The product expiry is (b) (4) months, as determined in the supplement review conducted by Dr. Pramoda Maturu on 28-Sep-2011. Supplement S003 for NDA 201-444 requested an expiry of 24 months, it is currently under review, the expiry determined applies to this NDA.

C. Basis for Approvability or Not-Approval Recommendation

This new NDA for the sodium nitrite individual components of the kit, sodium nitrite and sodium thiosulfate injection, is referenced to the already approved NDA 201-444 for support of approval. There are no updates to the CMC portion of the application(s), except for the update of labeling for the individual components, which have to be administered sequentially for this indication.

III. Administrative**A. Reviewer's Signature**

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

XIAOBIN SHEN

01/31/2012

The NDA is recommended for approval from CMC perspective.

PRASAD PERI

01/31/2012

I concur