CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203923Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 203923 / sodium thiosulfate injection

PMR/PMC Description: Evaluate alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	04/31/2012
	Study/Trial Completion:	07/31/2012
	Final Report Submission:	08/31/2012
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

   Sodium nitrite and sodium thiosulfate, used sequentially, are indicated for the treatment of cyanide poisoning, a life-threatening condition. These products are approved in a convenience kit under NDA 201444/Nithiodote Injection, and are now being approved as separate products – while maintaining the original indication – for logistics/expiration dating reasons.

   The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been characterized or qualified. Based on a clinical risk: benefit analysis, complete characterization of the leachable(s) from the container closure and definitive risk assessment can be completed post-marketing.

   This PMC is identical to the PMC issued under NDA 201444.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3087587

The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been characterized or qualified. Hope will conduct pharmaceutical development studies to explore the possibility of using alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3087587

Hope will conduct pharmaceutical development studies to explore the possibility of using alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile. Robust extractable studies and stability data (including leachables) are required to support the manufacturing and packaging changes. Inverted (worst case) storage configurations and stress conditions will be examined. Qualification or safety justifications will be required for leachables from these manufacturing changes.

a. Alternative container closure systems may include alternative rubber stoppers (b) (4), different glass vial sources, and (b) (4) bottles.
b. Alternative methods of (b) (4) sterilization such as (b) (4) will be investigated. Any manufacturing changes will be validated in context of the expected microbial load.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?

Reference ID: 3087587

☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3087587

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

/s/

MATTHEW W SULLIVAN
02/14/2012

JUDITH A RACOOSIN
02/14/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203923 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: <none> Established/Proper Name: sodium thiosulfate Dosage Form: injection Strengths: 250 mg/mL.		
Applicant: Hope Agent for Applicant (if applicable):		
Date of Application: 1/10/2012 Date of Receipt: 1/10/2012 Date clock started after UN:		
PDUFA Goal Date: November 10, 2012	Action Goal Date (if different): February 14, 2012	
Filing Date: March 10, 2012	Date of Filing Meeting: January 17, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of acute cyanide poisoning		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

Reference ID: 3087432

☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): PIND 78597

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required

Reference ID: 3087432

If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		Per OGD, this would not be a 505(j)
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	X			Per Henry Startzman in orphan products. As long as the labeling is the same/combo use only, Hope can come in under the original orphan designation. They would not get a new period of orphan exclusivity. They would get what is remaining on the Nithiodote approval.

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 201444	**Nithiodote**	**ODE**	**Jan 14, 2018**

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	X			Per Henry Startzman in orphan products. As long as the labeling is

Reference ID: 3087432

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				the same/combo use only, Hope can come in under the original orphan designation. They would not get a new period of orphan exclusivity. They would get what is remaining on the Nithiodote approval.

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	X			See above
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Reference ID: 3087432

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21	X			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Reference ID: 3087432

CFR 314.53(c)?				
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*		X		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

Reference ID: 3087432

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Reference ID: 3087432

REMS	YES	NO	NA	Comment
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

Reference ID: 3087432

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		DDMAC reviewed the previously-approved PI (NDA 201444) on January 10, 2011. The label submitted under this NDA is nearly identical to that of NDA 201444.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		

Reference ID: 3087432

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

Reference ID: 3087432

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 17, 2012

BLA/NDA/Supp #: 203923

PROPRIETARY NAME: <none>

ESTABLISHED/PROPER NAME: Sodium thiosulfate

DOSAGE FORM/STRENGTH: 250 mg / ml injection

APPLICANT: Hope Pharmaceutical

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of acute cyanide poisoning

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matt Sullivan	
	CPMS/TL:	Sara Stradley Parinda Jani	
Cross-Discipline Team Leader (CDTL)	Arthur Simone		
Clinical	Reviewer:	Arthur Simone	
	TL:	Rigo Roca	
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Reference ID: 3087432

Clinical Pharmacology	Reviewer:	David Lee	
	TL:	Yun Xu	
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	
	TL:	Dan Mellon	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xiaobin Shen	
	TL:	Danae Christodoulou Prasad Peri	
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (carton labeling)	Reviewer:	Denise Baugh	
	TL:	Lubna Merchant	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Reference ID: 3087432

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

Reference ID: 3087432

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Reference ID: 3087432

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Reference ID: 3087432

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Rigoberto Roca **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

Reference ID: 3087432

	• notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Reference ID: 3087432

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

Reference ID: 3087432

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Reference ID: 3087432

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

/s/

MATTHEW W SULLIVAN
02/14/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 203923	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: <none proposed> Established/Proper Name: sodium thiosulfate Dosage Form: injection Strengths: 250 mg/mL		
Applicant: Hope Pharmaceuticals		
Date of Receipt: January 10, 2012		
PDUFA Goal Date: November 10, 2012	Action Goal Date (if different): February 1, 2012	
Proposed Indication(s): for the treatment of acute cyanide poisoning		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Sodium Thiosulfate Injection, USP NDA 020166	Agency's previous findings of risk/benefit.
Magnesium Sulfate Injection NDA 19316	Sulfate levels in the sodium thiosulfate product
Sodium Chloride Injection NDA 18803	Total organic carbon for sodium thiosulfate

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed

Reference ID: 3085918

products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

As the proposed and referenced products are to be administered via the IV route of administration (100% bioavailable) with the same amount of active ingredients, the Agency waived the CFR's requirement for the submission of in vivo BA/BE data needed to bridge to the Agency's previous findings of safety and efficacy for sodium thiosulfate used in conjunction with sodium nitrate via NDA 020166. The sponsor justified the safety of the levels of sulfate in their drug product via reference to sulfate levels in the approved magnesium sulfate injection product as per the dosing and administration section of the label. To justify the levels of the total organic carbon, the sponsor analyzed levels in the referenced drug product and provided the data necessary to support the biowaiver request and scientific bridge to their product. These approaches were deemed scientifically valid and adequate by the review team.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Reference ID: 3085918

Sodium Thiosulfate Injection, USP	NDA 020166	Yes
Sodium Chloride Injection	NDA 018803	Yes
Magnesium Sulfate Injection	NDA 019316	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Sodium Thiosulfate Injection

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the

Reference ID: 3085918

archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

   Nithiodote was approved as a convenience kit of both Sodium Nitrite and Sodium Thiosulfate for the treatment of cyanide poisoning. This application provides for the packaging of Sodium Thiosulfate, alone, for the treatment of cyanide poisoning when used in conjunction with Sodium Nitrite.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

   *(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

   ***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

   YES ☒ NO ☐

   *If "**NO**" to (a) proceed to question #11.*
   *If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

   YES ☒ NO ☐

   (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

   YES ☒ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

Reference ID: 3085918

*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

Reference ID: 3085918

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

Reference ID: 3085918

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Reference ID: 3085918

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

/s/

MATTHEW W SULLIVAN
02/10/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	January 23, 2012
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strengths	Sodium Nitrite Injection, USP 300 mg/10 mL (30 mg/mL) Sodium Thiosulfate Injection, USP 12.5 grams/50 mL (250 mg/mL)
Application Type/Number	NDA 203922 NDA 203923
Applicant	Hope Pharmaceuticals, Inc.
OSE RCM #:	2012-117

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Sodium Nitrite Injection, USP, 300 mg/10 mL (NDA 203922) and Sodium Thiosulfate, USP, 12.5 grams/50 mL (NDA 203923) for areas of vulnerability that could lead to medication errors. These NDAs provide for separate packaging of individual components of Nithiodote which was approved on January 14, 2011.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed the container label, carton and insert labeling (OSE Review # 2010-1361 dated September 1, 2010) for NDA 201444. This NDA proposed the co-packaging of one vial each of Sodium Nitrite and Sodium Thiosulfate within a carton. Subsequently, a teleconference was held December 16, 2011 where the Applicant proposed to separate the vials so that they could be purchased individually. The reason for this is because the drug products do not have the same expiration dating and co-packaging them does not allow for inventory flexibility for purchasers. Hence, the carton and insert labeling for Sodium Nitrite and Sodium Thiosulfate were given separate NDA's (203922 and 203923, respectively) and submitted for our review for vulnerabilities to medication errors.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 10, 2012 insert labeling submission:

	Sodium Nitrite Injection, USP (NDA 203922)	Sodium Thiosulfate Injection, USP (NDA 203923)
Indication of use:	Sodium nitrite is indicated for sequential use with sodium thiosulfate for treatment of acute cyanide poisoning that is judged to be life-threatening	Sodium thiosulfate should be given following the administration of sodium nitrite for treatment of acute cyanide poisoning that is judged to be life-threatening
Route of administration	intravenous	intravenous
Dosage Form and Strength	One 10 mL vial of Sodium Nitrite Injection, USP which contains 30 mg/mL (300 mg/10 mL)	One 50 mL vial of Sodium Thiosulfate, USP which contains 250 mg/mL (12.5 grams/50 mL)
Dose	Administer 10 mL of Sodium Nitrite intravenously at a rate of 2.5 mL/minute to 5 mL/minute. Immediately thereafter, inject 50 mL (12.5 grams) of sodium thiosulfate. For pediatric	Administer 10 mL of Sodium Nitrite intravenously at a rate of 2.5 mL/minute to 5 mL/minute. Immediately thereafter, inject 50 mL (12.5 grams) of sodium thiosulfate. For pediatric

Reference ID: 3075624

	patients, the recommended dose of sodium nitrite is 6 to 8 mL/m^2 of body surface area (approximately 0.2 mL/kg of body weight) not to exceed 10 ml (300 mg); The recommended pediatric dose of sodium thiosulfate is 30 to 40 mL/m^2 of body surface area (approximately 1 mL/kg of body weight) but dosage should not exceed 50 mL (12.5 grams).	patients, the recommended dose of sodium nitrite is 6 to 8 mL/m^2 of body surface area (approximately 0.2 mL/kg of body weight) not to exceed 10 ml (300 mg); The recommended pediatric dose of sodium thiosulfate is 30 to 40 mL/m^2 of body surface area (approximately 1 mL/kg of body weight) but dosage should not exceed 50 mL (12.5 grams).
How Supplied	One 10 mL glass vial of sodium nitrite injection 30 mg/mL (containing 300 mg of sodium nitrite)	One 50 mL glass vial of sodium thiosulfate injection 250 mg/mL (containing 12.5 grams of sodium thiosulfate)
Storage	Controlled room temperature between 20°C and 25°C (68°F and 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); protect from light; do not freeze	Controlled room temperature between 20°C and 25°C (68°F and 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); protect from light; do not freeze
Container and Closure System	The primary container closure system is 50 cc, 20 mm United States Pharmacopeia (USP) Type 1 (b) (4) glass, (b) (4)	The primary container closure system is 50 cc, 20 mm United States Pharmacopeia (USP) Type 1 (b) (4) glass, (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 30, 2011 (which were previously approved under NDA 201444)
- Proposed Carton Labeling submitted January 10, 2012

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 3075624

- Insert Labeling submitted January 10, 2012
- Approved Carton Labeling (for NDA 201444) submitted June 30, 2011

Additionally, since Sodium Nitrite and Sodium Thiosulfate are currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Sodium Nitrite and Sodium Thiosulfate. The January 17, 2012, AERS search was conducted using the following search terms: active ingredient "Sodium Nitrite" and "Sodium Thiosulfate", and verbatim terms "sodium nitri%" and "sodium thios%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". Since a similar search was conducted August 18, 2010 with a previous review (OSE Review # 2010-1360 dated October 8, 2010), the time frame of the search was limited to August 19, 2010 to January 17, 2012.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error, involved concomitant medications, and dose omission likely related to knowledge deficit (e.g., user did not read insert labeling).

Following exclusions as outlined above, we found no cases relevant to this review.

3 ASSESSMENT OF MEDICATION ERROR POTENTIAL OF THE PROPOSED PRODUCT

The following sections describe the risk assessment of the proposed product design as well as the associated label and labeling.

3.1 PRODUCT DESIGN

Since the Applicant proposes the separation of the containers which would be used to treat cyanide poisoning, we considered the risk of medication errors with this product design. Specifically, we considered the risk that selection of the appropriate treatment would be compromised, either by giving only one of the products or selecting two vials with the same active ingredient. We provide recommendations in Section 4 to address some of these concerns.

3.2 LABELS AND LABELING

1. The Sodium Nitrite and Sodium Thiosulfate carton labeling both utilize similar (b) (4) layout on the principal display, side and rear panels and look almost identical to each other. In addition they also look identical to the approved Nithiodote carton labeling which contain both products packaged together. This similar presentation may cause confusion and lead to selection errors. Although both sodium nitrite and sodium thiosulfate should be used together to effectively treat cyanide poisoning, this presentation may increase the risk that the user will erroneously choose two vials with the same active

Reference ID: 3075624

ingredient because of their similar appearance. Therefore, differentiating between these two products by using different colors may help to minimize the risk of this type of error.

Additionally, in view of the proposal to provide these vials separately, there is the risk that only one of them is given for the treatment of cyanide poisoning. This is likely to minimize the effectiveness of the intervention and risk the patient's survival. Adding a statement to the carton labeling which reinforces the use of the two vials for effective treatment may mitigate this risk.

2. We note that one of the side panels is entirely (b) (4) information is presented in thin, (b) (4) font making it difficult to read. Additionally, this panel lacks a strength statement and therefore, this side of the carton labeling lacks important identifying information for this drug product.

3. In our assessment of the insert labeling, we noted that the dosage and administration information is different between the Highlights of Prescribing Information section versus the Full Prescribing Information section, that the established name for Sodium Thiosulfate Injection, USP is presented incorrectly, and that the statement regarding the inspection of parenteral drug products is incomplete. See Section 4 for our recommendations.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval of this NDA:

A. Carton Labeling (Sodium Nitrite Injection, USP and Sodium Thiosulfate Injection, USP)

1. The Sodium Nitrite and Sodium Thiosulfate carton labeling both (b) (4) look almost identical to each other. In addition, they also look identical to the approved Nithiodote carton labeling. To avoid selection errors, (b) (4) the approved container labels such that these cartons are distinguishable from each other and from the approved Nithiodote.

2. Delete the statement (b) (4) on the back panel (under Dosing & Administration heading) and add (b) (4) in this location. Additionally, improve the prominence of this information by bolding or adding color or by other means.

3. One of the side panels is entirely (b) (4) and information is presented in thin, (b) (4) font making it difficult to read. Revise the information on the (b) (4) side panel so that it is more prominent and visible to the reader. In addition, add the statement of strength to this panel so that this information is visible on all sides of the carton labeling.

Reference ID: 3075624

4. Add the statement 'Use with Sodium Thiosulfate (or Nitrite) for treatment of Cyanide Poisoning' to the principal display panel. Additionally, we recommend you box this statement.

5. Delete the statement (b) (4) which is stated in black font on the principal display panel as this information is redundant to the statement of strength already on the principal display panel. (Deletion of this statement will also allow space for recommendation #4 above).

6. Delete the statement which begins with (b) (4) as this information clutters the label and is stated in the insert labeling.

7. Increase the font size of the strength statement to increase its readability.

8. Revise the statement (b) (4) to read "Directions for Use: See Back Panel or Package Insert" to reflect both sources of information.

B. Insert Labeling

1. Sodium Thiosulfate Injection, USP (NDA 203923)

   a. Revise the established name (b) (4) to "Sodium Thiosulfate Injection, USP" in the Highlights of Prescribing Information Section

   b. Revise the Dosage and Administration Section located in the Full Prescribing Information Section such that the dosing information is the same as that in the Highlights of Prescribing Information Section.

   c. Revise the statement "All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration" to "All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit".

2. Sodium Nitrite Injection, USP (NDA 203922) - See comments B1b and B1c

If you have further questions or need clarifications, please contact Danyal Chaudhry OSE Project Manager, project manager, at 301-796-3813.

Reference ID: 3075624

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

/s/

DENISE V BAUGH
01/23/2012

LUBNA A MERCHANT
01/23/2012

CAROL A HOLQUIST
01/23/2012