CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	201-444
Supporting document/s:	SDN-23, -24, and -25
Applicant's letter date:	November 19, 2010, December 6, 2010, and December 22, 2010
CDER stamp date:	November 22, 2010, December 6, 2010, and December 22, 2010
Product:	Nithiodote (sodium nitrite and sodium thiosulfate co-packaged)
Indication:	Treatment of (b) (4) cyanide poisoning
Applicant:	Hope Pharmaceuticals
Review Division:	Division of Anesthesia and Analgesic Products (DAAP)
Reviewers:	Marcus S. Delatte, Ph.D. R. Daniel Mellon, Ph.D.
Supervisor/Team Leader:	R. Daniel Mellon, Ph.D.
Division Director:	Bob A. Rappaport, M.D.
Project Manager:	Allison Meyer

Template Version: September 1, 2010

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described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 201-444.

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1 Executive Summary

1.1 Introduction/Background

In February 1992, the Agency approved NDA 020166, an application for the marketing approval for intravenous sodium thiosulfate for the treatment of cyanide poisoning. This approval was based on the use sodium thiosulfate when used in conjunction with sodium nitrite. Based on the Agency's findings of safety and effectiveness for this product and the published literature, the Agency advised the current Applicant that applications for the administration of sodium thiosulfate and sodium nitrate, 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 and efficacy of the two products (see pre-IND meeting minutes; July 2007). Within this context, the Agency advised the Applicant that the approval of an NDA application for these two components would depend on the adequacy of the chemistry, manufacturing, and controls (CMC) data provided and the related inspections conducted. Based on the advice provided, the applicant submitted NDA 201-444 as a 505(b)(2) application for their product Nithiodote, which contains these two drug products, for the treatment of [redacted] (b) (4) cyanide poisoning (see May 2010 submission). Upon review, the Agency determined that the application could not be approved in its original form. In a letter mailed on November 18, 2010, the Applicant was informed that the Agency took a **Complete Response** action on NDA 201-444. This letter described the reason for the Agency's action and, where possible, its recommendations to address these issues (see excerpt below from the correspondence)

> **Deficiency:** You have not provided adequate characterization of the [redacted] (b) (4) leachate(s) in the drug products in order to conduct an adequate risk assessment for your product and justify your proposed product expiry. In order to resolve this deficiency you may consider the following options:
>
> **Option 1:**
>
> 1. Establish the identity, source, and mass balance of the [redacted] (b) (4) leachate(s). Reasonable approaches may include the methods reported through your primary literature searches [redacted] (b) (4) A robust extractable study performed using the drug product solutions to extract all components of the container closure system will be required to address this deficiency.
>
> 2. Provide sufficient data to determine whether the leachable [redacted] (b) (4) material will continue to increase on storage and what the anticipated exposure will be. Again, a robust extractable study performed using the drug product solutions to extract all components of the container closure system is required.

3. Provide an adequate toxicological risk assessment for the identified (b) (4) leachable(s). This can be completed either via a new toxicology study or, if available, you may provide toxicology data from the literature to support the proposed exposure levels of the identified leachable(s), taking into consideration the route of administration. If definitive characterization of the (b) (4) leachables is not possible and adequate intravenous toxicology data is not available in the literature, we recommend conducting a single-dose intravenous toxicology study in a single species that includes both acute and delayed observations (24 hours and 14 days), using drug product at the end of the proposed shelf-life. The dosing protocol should result in exposure to (b) (4) compounds equal to or greater than that which will be administered to human via the use of drug product at the end of your proposed shelf life. The study should define a no adverse effect levels (NOAEL) or characterize acceptable toxicity for the proposed indication. Reference to comparable levels of exposure to a leachable via an FDA approved drug product(s) should be supported by actual data and appropriate 505(b)(2) patent certification.

Option 2:

4. Alternatively, you may propose a new container closure system that might have an acceptable leachable profile. Your search for a new container closure system might include, but should not be limited to, alternative rubber stoppers (e.g., (b) (4), different glass vial sources, and polypropylene bottles. With this option, a robust extractable study will be required, performed using the drug product solutions to extract all components of the container closure system. A minimum of six months of stability data (including leachables) using the new container closure system which includes results from testing at release, 3 months, and 6 months under real time storage and accelerated stability conditions will be required. Both conditions should include upright and inverted storage configurations. The extractable and leachable data from this new container system may be obtained from laboratory scale or pilot scale batches. Qualification or safety justifications will be required for leachable components from this new container closure system (refer to requirement #3 under Option 1).

On November 19, 2010, the Applicant submitted new information regarding (b) (4) levels in an FDA approved drug class that would result in comparable exposure levels to those which would occur via this product. The information was further described in the post-action meeting request/package dated December 6, 2010.

The Applicant met with the Agency for the post-action meeting on December 21, 2010 to discuss their proposal to address the deficiencies noted in the complete response letter. Following this discussion, the Applicant submitted their Complete Response for NDA 201-444 on December 22, 2010.

1.2 Brief Discussion of Nonclinical Findings

There were no new nonclinical data submitted in the Applicant's Complete Response for NDA 201-444. In their complete response, to address the concern regarding the lack of

clear safety data for the levels of (b) (4) materials leached into the drug products, the Applicant identified an additional FDA-approved drug product class that appears to contain (b) (4) leachables at comparable levels to those identified in this product. Specifically, the Applicant provided data demonstrating that the amount of (b) (4) (mcg) detected in a phenytoin sodium injectable drug product would result in a daily exposure that exceeds that which would occur via use of the sodium nitrite and sodium thiosulfate products if the phenytoin was dosed as labeled for the treatment of status epilepticus (see **Figure 1** below; reproduced from the Applicants December 20, 2010 submission) These data appear to support the Applicant's claim that (b) (4) (b) (4) leachates in the Nithiodote drug product are present at levels comparable to or greater than that in other products, as well as the findings from published studies that have demonstrated that variables such as drug pH (≥ 8) may facilitate the leaching of (b) (4) compounds from glass container closure systems (b) (4) (b) (4)

(b) (4)

However, the total daily exposure to (b) (4) via phenytoin injectable drug products

during the treatment of status epilepticus is comparable to the daily exposure that would occur via Nithiodote.

1.3 Recommendations

1.3.1 Approvability

Technically, the sponsor has not provided adequate characterization of the toxicological effects of intravenous infusion of the (b) (4) leachables detected in this drug product to conduct a toxicological risk assessment. However, they have provided information to suggest that individuals treated for status epilepticus with intravenous phenytoin products are apparently exposed to comparable levels of these leachables. Assuming the (b) (4) leachables from (b) (4) glass are of comparable chemical composition, given the potentially life-threatening indication and apparent lack of a safety signal from phenytoin injectable products, there does not appear to be a safety concern that would preclude approval of this product. However, as the Applicant's response is based on clinical experience with FDA approved drug products, the NDA may be approved at the discretion of the clinical review team.

1.3.2 Additional Nonclinical Recommendations

No nonclinical toxicology post marketing studies are recommended at this time, given the findings from the present application and the published literature, which suggest that drug products with a high pH may cause the leaching of (b) (4) chemicals from glass vials (b) (4) These findings impact multiple products regulated by the Agency and therefore, if deemed necessary following further internal discussions, the Agency will consider means to address this issue across the products affected. The Pharmacology Reviewers have discussed this issue within the nonclinical pharmacology and toxicology hierarchy of the Agency.

From a nonclinical perspective, further studies may be recommended pending review of the results of the confirmatory post-marketing quality assessments requested by the chemistry, manufacturing, and controls (CMC) review team.

1.3.3 Labeling

See action letter for final labeling.

Reference List

(b) (4)

[redacted]

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

/s/

MARCUS S DELATTE
01/10/2011

RICHARD D MELLON
01/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**201-444**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**21-May-2010**
PRODUCT:	**Nithiodote (Sodium nitrite, Sodium thiosulfate) injection**
INTENDED CLINICAL POPULATION:	**Treatment of** (b) (4) **cyanide poisoning**
SPONSOR:	**Hope Pharmaceuticals**
DOCUMENTS REVIEWED:	**N000 (EDR)**
REVIEW DIVISION:	**Division of Anesthesia and Analgesia Products (HFD-170)**
PHARM/TOX REVIEWERS:	**R. Daniel Mellon, Ph.D./Marcus S. Delatte, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Allison Meyer**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the nonclinical pharmacology and toxicology perspective, NDA 201-444 is deemed a complete response and can not be recommended for approval at this time. The following deficiency remains:

Due to the lack of definitive characterization of [redacted] (b) (4) compounds in the leachate and evidence of increasing levels of [redacted] with time, the Sponsor has not provided adequate data to allow a definitive toxicological risk assessment for the levels of leachable [redacted] (b) (4) compounds from the container closure system to support the proposed expiry.

B. Recommendation for nonclinical studies

The Sponsor must submit definitive intravenous toxicology data to support the safety of the levels of [redacted] (b) (4) compounds present in the drug products via the intravenous route of administration. We recommend conducting a single-dose intravenous toxicology study in a single species using drug product at the end of the proposed shelf-life that includes both acute and delayed observations (24 hours and 14 days). The dosing protocol should result in exposure to [redacted] (b) (4) compounds equal to or greater than that which will be administered to human via the use of drug product at the end of the proposed shelf life. The study should define a no adverse effect levels (NOAEL) or characterize acceptable toxicity for the proposed indication.

Alternatively, if the Sponsor can definitively identify the chemical composition of the [redacted] (b) (4) impurities, they may provide toxicology data from the literature to support the proposed exposure levels, taking into consideration the route of administration. If the information is not available in the literature, a toxicology study employing saline spiked with appropriate levels of the identified leachables could also be considered. If the sponsor wishes to reference an FDA approved product that when used would result in exposure to comparable levels the identified leachable the Sponsor should provide comparative data to support such claim and provide appropriate 505(b)(2) patent certification.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No new nonclinical toxicology studies were submitted in support of this NDA application with the exception of a single genetic toxicology study. The Sponsor is relying upon the Agency's previous findings of safety and efficacy of the sodium thiosulfate used in conjunction with sodium nitrite that were made upon review of NDA 20-166 to support the proposed use of two components on this drug product combination.

The revised chemistry, manufacturing and controls specifications for the drug products are adequately justified for safety. The leachable study for the rubber stopper in the container closure identified several compounds above the PQRI threshold of toxicological concern of 5 mcg/day for inhalation drug products. The exact chemical identity of the (b) (4) reported in the leachable study has not been determined; however, it is hypothesized that the (b) (4) is predominantly (b) (4), rather than (b) (4). Following extensive evaluations during the review cycle, there are several possible sources of (b) (4) such as (b) (4), only a portion of which appears to be derived from (b) (4) of the rubber stopper. Interestingly, there is a long history of use of these stoppers in FDA-approved parenteral products that provides some reassurance of safety; however, the high pH of this solution and chemical characteristics of these drug solutions present unique extraction conditions. Therefore, use in previously approved potential drug products does not provide adequate assurance of safety for this application.

B. Pharmacologic activity

Cyanide toxicity is believed to result primarily from inhibition of cytochrome oxidase, the terminal oxidase of the mitochondrial respiratory chain. Inhibition of cytochrome oxidase results in a blockade of aerobic metabolism and energy production leading to cellular hypoxia. Cyanide inhibition of cytochrome oxidase can be reversed either by sequestration or biotransformation of cyanide.

Sodium nitrite is classically thought to exert its protective effect by reacting with hemoglobin to form methemoglobin. Methemoglobin displaces cyanide from cytochrome oxidase, allowing resumption of aerobic metabolism.

The primary route of endogenous cyanide detoxification is by enzymatic transulfuration to thiocyanate (SCN^-), which is relatively nontoxic and readily excreted in the urine. Sodium thiosulfate is thought to serve as a sulfur donor

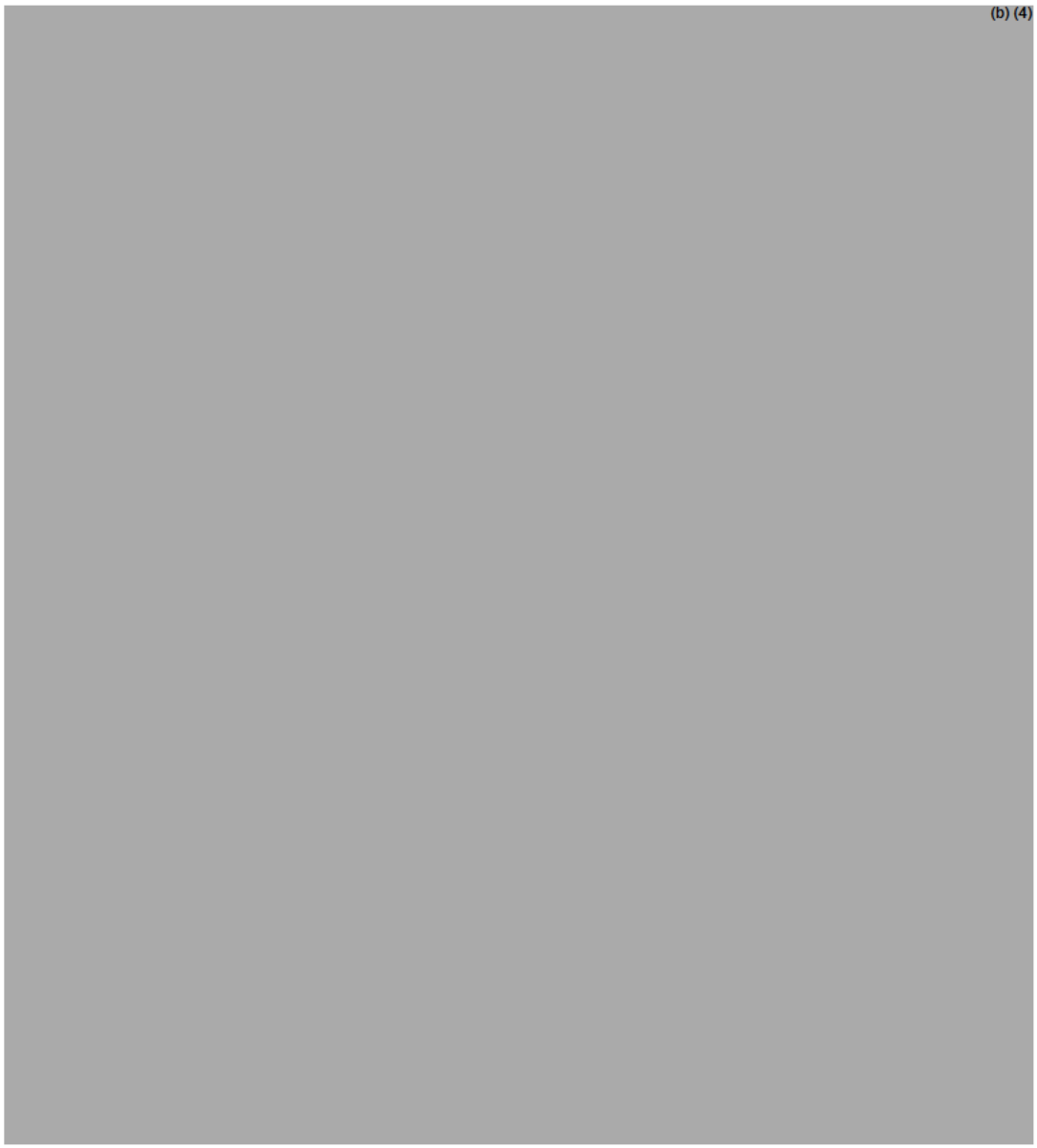
in the reaction catalyzed by the enzyme rhodanese, thus enhancing the endogenous detoxification of cyanide.

C. Nonclinical safety issues relevant to clinical use

Nonclinical safety issues related to the use of sodium thiosulfate in conjunction with sodium nitrite were previously evaluated during the review of the referenced NDA 20-166. In addition, the reviewers have reviewed the existing literature on the safety of these two agents, which is reflected in the proposed labeling. The results of this literature search indicate that sodium nitrite has tested positive in standard genetic toxicology studies and has been shown to have embryotoxic and developmental effects which should be taken in to consideration by medical practitioners when deciding on a course of treatment when cyanide poisoning is suspected.

The data obtained regarding potential leachables into the drug product solutions is difficult to interpret due to lack of definitive information regarding the chemical identity of the leachable (b) (4) compound(s). Adequate safety justification was obtained for the levels of (b) (4) However, the levels of (b) (4) identified in the four and six month stability studies appear to be increasing (b) (4) (b) (4). Although the analytical technique employed detects (b) (4), it is not certain what molecular form the (b) (4) detected is derived from. Based on the studies conducted to date, the (b) (4) appears to be derived from multiple sources and therefore may reflect exposure to several different chemicals, including (b) (4) (b) (4) Based on the six month leachable data, the total level of (b) (4) detected in one 50 mL vial of sodium thiosulfate includes (b) (4) from the stopper (likely (b) (4)), (b) (4) (b) (4) from the vial itself ((b) (4)), (b) (4) mcg from the drug substance itself (likely (b) (4) derived from manufacturing components), (b) (4) from the boric acid, (b) (4) from the potassium chloride, and (b) (4) from the sodium hydroxide. This accounts for a total of (b) (4) of (b) (4) leaving (b) (4) detected in the leachate unaccounted for (and (b) (4) of the total amount obtained via both drug products unaccounted for). It is possible that the remaining (b) (4) detected is derived from the (b) (4), which contains more than one (b) (4) per (b) (4) molecule, pending the molecular weight of the (b) (4) entities leached from the rubber stopper. The chemistry review team has recommended further studies to identify all the sources of (b) (4) and to explore alternative container closure systems. They have recommended a complete response.

From a toxicology perspective, any risk assessment is complicated by the fact that the exact chemical composition of the (b) (4) identified is unknown.



Although the Sponsor has provided some data to suggest that (b) (4) are likely leached from most parenteral glass vials, this is based on information from literature and no data were provided analyzing FDA approved drug products to put these findings into perspective. Collectively, there are data that suggest that the levels of (b) (4) in the leachates of this product may be within the upper range of that obtained via use of other FDA approved drug product formulations. If correct, there would appear to be relatively low risk given the proposed indication of this drug product. However, adequate data have not been provided in order to employ this rationale to support the safety of this product.

Overall, given the uncertainty of the chemical identification of the (b) (4) levels detected in the leachate, the most definitive toxicological assessment of safety would be accomplished via a single-dose intravenous toxicology study

in a single species using both drug products at the end of the proposed shelf-life that includes both acute and delayed endpoints (24 hours and 14 days).

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	201-444
Review number:	1
Sequence number/date/type of submission:	N000/21-May-2010/Original NDA N001/16-Jun-2010/Amendment N002/25-Jun-2010/Amendment N003/2-Jul-2010/Amendment N004/9-Jul-2010/Amendment N005/27-Jul-2010/Amendment N006/10-Aug-2010/Amendment N007/18-Aug-2010/Amendment N008/19-Aug-2010/Amendment N009/20-Aug-2010/Amendment N010/23-Aug-2010/Amendment N011/30-Aug-2010/Amendment N012/31-Aug-2010/Amendment N013/3-Sep-2010/Amendment N014/7-Sep-2010/Amendment N015/7-Sep-2010/Amendment N016/13-Sep-2010/Amendment N017/17-Sep-2010/Amendment N018/20-Sep-2010/Amendment N019/24-Sep-2010/Amendment N020/15-Oct-2010/Amendment N021/22-Oct-2010/Amendment
Information to sponsor:	Yes (X) No ()
Sponsor and/or agent:	Hope Pharmaceuticals Scottsdale, AR
Manufacturer for drug substance:	(b) (4) [redacted]

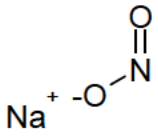
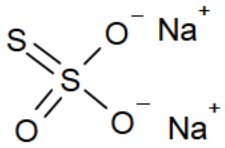
Reviewers names:	R. Daniel Mellon, Ph.D./Marcus S. Delatte, Ph.D.
Division name:	Division of Anesthesia and Analgesia Products (DAAP)
HFD #:	170

Drug:

Trade name:	Nithiodote
Generic name:	Sodium nitrite injection & sodium thiosulfate injection

Code name: Cyanide Antidote Kit

Table 1. Information on the drug products under review

Component	Sodium nitrite	Sodium thiosulfate
Chemical Name	Nitrous acid, sodium salt	Thiosulfuric acid, disodium salt
CAS number	7632-00-0	7772-98-7
Molecular formula	HNO_2•Na	O_3S_2•2Na
Molecular weight	69.00	158.13
Structure		
Manufacturer	(b) (4)	(b) (4)

Relevant INDs/NDAs/DMFs:

Table 2. Relevant NDA and IND applications

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
20-166	Sodium Thiosulfate	DAARP	250 mg/mL	Discontinued	14-Feb-1992	Cyanide Poisoning	US Army

IND#	Status	Division	Indication	Stamp Date	Sponsor
78,597	Preassignment	DAAP	Treatment of (b) (4) cyanide poisoning	14-May-2007	Hope Pharmaceuticals

Several DMFs were referenced in this NDA. See **Table 3** for further information.

Table 3. DMFs referenced by NDA 201-444

DMF#	Subject of DMF	Holder
(b) (4)	(b) (4)	(b) (4)

Drug class: Antidote

Intended clinical population: [redacted] cyanide poisoning

Clinical formulation: Each Cyanide Antidote Kit contains the following:

Table 4. Information on the contents of the Cyanide Antidote Kit

Component	Count, Container (Dosage)	Manufacturer
Sodium Nitrite Injection, USP	1 vial (300 mg in 10 mL water for injection)	[redacted]
Sodium Thiosulfate Injection, USP	1 vial (12.5 g in 50 mL of water for injection)	[redacted]
Set of instructions	1	[redacted]
Package insert	1	[redacted]

The compositions of the individual components are described by the sponsor in the tables below, reproduced from the submission (2.3.P.1 for Sodium Thiosulfate and Sodium Nitrite):

Figure 1. Components and composition of the **sodium nitrite injection drug product**

Ingredient	Function	Unit Formulation (per mL)	Unit Formulation (per 10 mL vial)
Sodium nitrite, USP	Active pharmaceutical ingredient	30.0 mg	300 mg
[redacted] USP	[redacted]	[redacted]	[redacted]
[redacted] NF			

Abbreviations: NF, National, Formulary; qs, quantity sufficient; USP, United States Pharmacopeia

Figure 2. Components and composition of the **sodium thiosulfate injection drug product**

Ingredient	Function	Unit Formulation (per mL)	Unit Formulation (per 50 mL vial)
Sodium thiosulfate, USP	Active pharmaceutical ingredient	250.0 mg	12.5 g
Potassium chloride, USP	[redacted]	4.40 mg	[redacted]
Boric acid, NF		2.80 mg	
Boric acid, NF			[redacted]
Sodium hydroxide, NF			
[redacted] USP			
[redacted] NF			

Abbreviations: NF, National Formulary; qs, quantity sufficient; USP, United States Pharmacopeia; [redacted]

Impurity profile

Based on the review of the specifications listed (see below), several impurities were proposed at levels above that original suggested by the Agency for the drug substance. To address the safety of these proposed specifications, the Sponsor provided justifications (see **Table 5**) for the levels of the impurities that exceeded those recommended by the Agency. See below for these justifications and comments provided by the Pharmacology/Toxicology Reviewers. Overall, these justifications appear reasonable and were deemed acceptable by the Pharmacology/Toxicology Reviewers.

Figure 3. Comparison of FDA recommended and Hope proposed specifications for the **sodium nitrite drug substance** (excerpt from 3.2.S.4.5, page 3)

Test	Method	FDA Recommended Acceptance Criteria	Hope Proposed Acceptance Criteria
Appearance	Visual	-	(b) (4)
Identification Sodium Nitrite	 USP <191> USP <191>	 Passes Test Passes Test	 Passes Test Passes Test
Loss on drying	USP<731>	(b) (4)	(b) (4)
Heavy metals (as Pb)	USP<231>		
Assay	PHR-177 (HPIC)		
Sodium nitrate	PHR-177 (HPIC)		
pH (10% w/w solution at 25°C)	USP<791>		
(b) (4)	USP<921> KF		
	PHR-208		
	ACS 10		
	ACS 10		
	ACS 10		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	CH-PRO-289		
Residual solvents (b) (4)	SOP T424 (GC)		
Residual (b) (4)	061209/001 (LC-MS/MS)		
Bacterial endotoxins	USP<85>		
Microbial limits Aerobic count Yeast and mold	 USP<61>		

Abbreviations: ACS, American Chemical Society; cfu, colony forming unit; EU, endotoxin units; GC, gas chromatography; HPIC, high performance ion chromatography; ICH, International Conference on Harmonisation; ICP-MS, inductively coupled plasma mass spectroscopy; KF, Karl Fischer, LC-MS/MS, liquid chromatography tandem mass spectroscopy; NMT, not more than; SOP, standard operating procedure; (b) (4) (b) (4) USP, United States Pharmacopeia.

Figure 4. Specifications proposed by Hope for the **sodium nitrite drug product** (excerpt from 3.2.P.5.1, page 1)

Test	Method	Acceptance Criteria
Appearance	Visual	(b) (4)
Identification Sodium Nitrite	 USP<191> USP<191>	
pH	USP<791>	
Assay	PHR-177 (HPIC)	
Related substances (b) (4)	PHR-177 (HPIC)	
	PHR-190	
Sterility	USP<71>	
Particulate matter in injections	USP<788>	
Bacterial endotoxins	USP<85>	
Net contents	USP<1>	

Abbreviations: EU, endotoxin units; HPIC, high performance ion chromatography; NMT, not more thar (b) (4)
(b) (4) USP, United States Pharmacopeia

Figure 5. Comparison of FDA recommended and Hope proposed specifications for the **sodium thiosulfate drug substance** (excerpt from 3.2.S.4.5, page 5)

Test	Method	FDA Recommended Acceptance Criteria	Hope Proposed Acceptance Criteria
Appearance	Visual	Colorless crystals	(b) (4)
Identification	USP monograph	Color is discharged	
Identification Sodium Thiosulfate	 USP <191> USP <191>	(b) (4)	
Assay	PHR-178 (HPIC)		
Loss on drying	USP<921>		
Heavy metals	USP<231>		
Odor	Olfactory		
pH of 10% solution	USP<791>		
Appearance of 10% solution	USP<641>		
Insoluble matter	ACS 10		
(b) (4)	PHR-188 (HPIC)		
	PHR-188 (HPIC)		
	PHR-188 (HPIC)		
	PHR-189 (ACS 10)		
	PHR-210		
	USP<251>		
	ACS 10		
	CH-PRO-294-01		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	ICP-MS		
	AA		
Bacterial endotoxins	USP<85>		
Microbial limits Aerobic count	USP<61>		

Figure 6. Proposed specifications for the **sodium thiosulfate drug product** (excerpt from S.2.P.5.1, page 1)

Test	Method	Acceptance Criteria
Appearance	Visual	Clear and colorless
pH	USP<791>	7.5-9.5
Identification Sodium Thiosulfate	 USP <191> USP <191>	 Passes Test Passes Test
Assay	PHR-178 (HPIC)	(b) (4)
(b) (4)	PHR-188 (HPIC)	NMT (b) (4) NMT
	PHR-189 (ACS 10)	NMT (b) (4)
Sterility	USP<71>	Sterile
Particulate matter in injections	USP<788>	NMT (b) (4) NMT
Bacterial endotoxins	USP<85>	NMT (b) (4)

Abbreviations: EU, endotoxin units; HPIC, high performance ion chromatography; NMT, not more than; USP, United States Pharmacopeia.

Table 5. Lists impurities that exceeded the drug substance specifications proposed by the Agency

Drug Substance	Impurity	Amount measured in product	Justification to support the safety of the impurity
Sodium nitrite (450 mg or 7.5 mg/kg)	(b) (4)	(b) (4)	(b) (4)
			(b) (4)
			(b) (4)

Drug Substance	Impurity	Amount measured in product	Justification to support the safety of the impurity
		(b) (4)	(b) (4)
Sodium thiosulfate (18.75 g or 312.5 mg/kg)	(b) (4)		

Drug Substance	Impurity	Amount measured in product	Justification to support the safety of the impurity
			(b) (4)

Table 6. Safety margins determined using NOAELS established in animals from repeat-dose toxicology studies

[redacted]							
Authors	**Species**	**Duration (weeks)**	**Sex**	**NOAEL (mg/kg)**	**NOAEL (mg/m^2)**	**Human Dose (0.008 mg/kg) as mg/m^2**	**Safety Margin based on mg/m^2 (animal NOAEL/human dose)**
Maita et al. (1981)	Rat	13	M	234	1404	0.37	3794 X
			F	243	1458	0.37	3940 X
	Mouse	13	M	458	1374	0.37	3713 X
			F	479	1437	0.37	3883 X

Extractable Studies

Studies were conducted to investigate the extractables derived from the [redacted] sodium thiosulfate and the [redacted] rubber stoppers used to package the pharmaceutical products under review.

The [redacted] sodium thiosulfate was evaluated using a quantitative estimate and qualitative characterization of possible leachates in this product (Study No. 08-232E). The extractions studies used two separate procedures (i.e., [redacted]). In the [redacted]

To test for leachates, filter and control samples were evaluated using [redacted] The Sponsor reported that some leachable peaks may have been masked [redacted] and not detected. [redacted] All of the extractables were recovered, which served to qualify the procedure. No leachate peaks were detected

in the analysis of sodium thiosulfate samples after contact with the [redacted]

The [redacted] stoppers are the subject of two [redacted] DMFs [redacted] and have been previously deemed adequate for use in numerous FDA-approved parenteral drug products. These stoppers meet the requirements outlined in general chapter ‹381› of the USP, Elastomeric Closures for injection including negative results in the USP biological reactivity studies.

The [redacted] stoppers were extensively evaluated by [redacted] on the behalf of Hope Pharmaceuticals. These stoppers were evaluated using [redacted] (see **Figure 7**).

To evaluate the biological reactivity of the extractables detected the Sponsor studied the potential cytotoxicity, intracutaneous toxicity in rabbits, and systemic toxicity in mice treated with extracts obtained from the [redacted] stoppers. Cytotoxicity of the separate extracts was evaluated by using the iso elution method. In these studies, L-929, mouse fibroblast cells were propagated and maintained in open wells. [redacted] culture wells were used by the Sponsor. The growth medium contained in these wells was replaced with two mL of test extract [redacted]) and incubated at 37°C in 5% CO_2 for 48 hours. Following this incubation period, the cultures were examined microscopically (100X) to evaluate percent lysis and their cellular characteristics. The test extracts reportedly did <u>not</u> show any evidence of causing cell lysis or toxicity. In vivo studies were conducted to determine the potential systemic (mice; **TU012-500**) and intracutaneous toxicity (rabbits; **TU013-800**) of the [redacted] The [redacted] was reportedly extracted in 0.9% sodium chloride and [redacted]. In mice (n=5/group), the extract (50 mL/kg) was administered either intravenously or intraperitoneally for evaluation. Five mice were similarly injected with the corresponding control. These animals were observed four, twenty four, forty eight, and seventy two hours after treatment. At these time points, endpoints such as body weight, mortality and clinical signs were recorded. Based on findings from these observations, the extract in mice reportedly did <u>not</u> produce mortalities or any evidence

of systemic toxicity following intravenous or intraperitoneal administration. In rabbits (n=2), the extract (0.2 mL) was administered intracutaneously for evaluation. Rabbits were administered 0.2 mL of extract and control blank, respectively, into five separate sites (2 cm apart) on the right and left side of their back. These animals were observed for erythema and edema at these sites twenty-four, forty-eight, and seventy-two hours after injection. Based on findings from these observations, the extract in rabbits reportedly did not produce evidence of irritation or any other apparent toxicities following intracutaneous administration.

Figure 7. Lists of the extractables detected by the Sponsor

Table 1 Assignments and approximate amounts (µg) for the (b) (4) extractables from the stoppers.

Time	Assignment[a]	Approximate Amount (µg per stopper)[b] (b) (4)
		(b) (4)

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Leachables study

According to the Sponsor, [redacted] has conducted leachates testing on the drug product stoppers by using inverted stability samples at the four-month time point for accelerated samples (see **3.2.P.2.4.2**; results discussed below). Note that preliminary findings at the six-month time period have been provided by the Sponsor and that further analyses are planned at the six-, nine-, and twelve-month stability time points. Leachates in the four-month drug stability samples were assayed by the following techniques:

- **Gas chromatography-mass spectrometry** analysis of
  - [redacted] extracted drug products
  - [redacted] drug products
  - Headspace of the drug products
- **Gas analysis-mass spectrometry** analysis of
  - [redacted] drug products
- **Inductively coupled plasma optical emission spectroscopy** and **inductively coupled plasma mass spectrometry** and **ion chromatography** analyses
- **Liquid chromatography atmospheric pressure ionization mass spectroscopy** analysis
- **Liquid chromatography electrospray mass spectrometry** analysis

Based on findings from this testing, the Sponsor reported that leachates were detected in the two drug products proposed for marketing approval based on findings from studies using the detection methods mentioned above. In the initial leachable studies evaluating samples the sodium thiosulfate drug product (from the four-month inverted accelerated stability samples), the Sponsor reported [redacted] were the only leachates detected above the PQRI recommended 5 mcg/day threshold for qualification for inhalation drug products. Separately, in the initial leachables studies evaluating the sodium nitrate drug product, this method was used and [redacted] was detected, but the amount was less than the limit of detection [redacted] According to the Sponsor, interference by [redacted] in the drug product may have limited the findings with the inductively coupled plasma optical emission spectroscopy (ICP-OES) method. Given that a quantitative estimate of [redacted] in the sodium nitrate drug product could not be provided using this method, and the lack of reliable findings on its levels, the Sponsor decided to assay levels of this element in both drug products by using the inductively coupled plasma mass spectrometry (ICP-MS) method instead. In the sodium nitrate drug product, [redacted] was detected in the four-month (inverted accelerated stability) samples [redacted] as well as in the six-month samples [redacted] Based on the maximum dose of sodium nitrate proposed, [redacted] exposure at its highest value detected [redacted] by the ICP-MS method equals [redacted] in this product alone. In the sodium thiosulfate drug product, [redacted] was detected in the four-month sample at [redacted] and in the six-month sample [redacted]. Based on the maximum proposed dose of sodium thiosulfate proposed, [redacted] exposure at its highest level detected [redacted] by the ICP-MS method equals [redacted] in this product alone. Note that the total amount of [redacted] in these products combined equals [redacted] when based on values from samples that detected the highest level of the element

in each drug product. Given the levels of the (b) (4) and the other (b) (4) leachates mentioned, the Sponsor provided a risk assessment based on findings from reports provided by the Environmental Protection Agency (i.e., EPA; see (b) (4)); World Health Organization (see (b) (4) U.S. Department of Health and Human Services (see (b) (4) and the National Toxicology Program (see (b) (4) ; as well as from various published studies in the literature. These findings and those obtained by the PT Reviewers were reviewed prior to writing the risk assessment for the (b) (4) leachates detected at levels above the PQRI threshold (see below).

(b) (4)

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In conclusion, the Sponsor reported that these leachates do not represent a safety concerns at the levels detected in the drug products when compared to levels of exposure in published findings submitted as part of the application under review. Based on a review of the published literature the Reviewers concur with the Sponsor that the levels of (b) (4), at the levels detected, appear to be safe. Note that the daily amount of leachate exposure was estimated based on the highest dose recommended for these products. Although the published toxicology literature identified employ alternative routes of administration, systemic exposure to these compounds is anticipated and given the very large safety margins, the oral toxicology data is deemed adequate. In contrast, the safety justification of (b) (4) is confounded by the lack of clear data with respect to the chemical composition of the leached material and the lack of absorption of (b) (4) via the oral route to provide clear coverage for the safety via the IV route.

Route of administration: Sodium thiosulfate and sodium nitrite are proposed for use via the intravenous route of administration.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

For (b)(2) applications:

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 201-444 are owned by Hope Pharmaceuticals or are data for which Hope Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 201-444 that Hope Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Hope Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 201-444.

The sponsor is submitting a 505(b)(2) NDA relying upon the Agency's previous finding of safety and efficacy of sodium thiosulfate used in conjunction with sodium nitrite (NDA 20-166) as well as literature references.

Studies reviewed within this submission: A single genetic toxicology study was submitted as new nonclinical pharmacology or toxicology studies for this NDA application.

Studies not reviewed within this submission: N/A

Product History and Background: A three component cyanide antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate) was marketed by Eli Lilly as early as 1944. Eli Lilly no longer markets this product; and Akorn is the current supplier of this kit. A search of the web notes that one can obtain a similar kit from ABO Pharmaceuticals (distributor: http://www.abopharmaceuticals.com/cyanide_kit.shtml?gclid=CIauzZjD348CFQUsPAodEBkH8g). Emergency Medical Products, Inc. supplies a Taylor Pharmaceutical Cyanide Antidote Kit of comparable composition (http://www.buyemp.com/product/1124401.html). None of these kits have been officially approved by the FDA.

The FDA has approved a different product, Cyanokit (EMD Pharmaceuticals), which contains hydroxocobalamin (NDA 22-041) on December 15, 2006. The FDA has also approved sodium thiosulfate for use in conjunction with sodium nitrite for the treatment of cyanide poisoning (NDA 20-166) on February 14, 1992.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Cyanide toxicity is believed to result from its inhibition of cytochrome oxidase, the terminal oxidase of the mitochondrial respiratory chain. Inhibition of cytochrome oxidase results in a blockade of aerobic metabolism and energy production leading to cellular hypoxia. Cyanide inhibition of cytochrome oxidase can be reversed either by sequestration or biotransformation of cyanide.

Sodium Nitrite

Sodium nitrite is classically thought to exert its protective effect by reacting with hemoglobin to form methemoglobin, an oxidized form of hemoglobin incapable of oxygen transport but with high affinity for cyanide. Cyanide preferentially binds to methemoglobin over cytochrome a_3, forming the nontoxic cyanmethemoglobin. Methemoglobin displaces cyanide from cytochrome oxidase, allowing resumption of aerobic metabolism. The chemical reaction is as follows:

$$NaNO_2 + \text{Hemoglobin} \rightarrow \text{Methemoglobin}$$

$$HCN + \text{Methemoglobin} \rightarrow \text{Cyanmethemoglobin}$$

Sodium Thiosulfate

The primary route of endogenous cyanide detoxification is by enzymatic transulfuration to thiocyanate (SCN^-), which is relatively nontoxic and readily excreted in the urine. Sodium thiosulfate is thought to serve as a sulfur donor in the reaction catalyzed by the

enzyme rhodanese, thus enhancing the endogenous detoxification of cyanide in the following chemical reaction:

$$Na_2S_2O_3 + CN^- \xrightarrow{\text{Rhodanese}} SCN^- + Na_2SO_3$$

Drug activity related to proposed indication: No new nonclinical efficacy studies were submitted to support the proposed NDA.

2.6.2.3 Secondary pharmacodynamics

Vasodilation has also been cited to account for at least part of the therapeutic effect of sodium nitrite, since cardiovascular and respiratory changes are reported before the formation of significant amounts of methemoglobin (Vick and Froehlich, 1985).

2.6.2.4 Safety pharmacology

Safety pharmacology studies were not submitted for any component of the kit alone or in combination. As these drugs have previously been used in humans, such studies are not deemed critical to this NDA application.

2.6.2.5 Pharmacodynamic drug interactions

The combination of sodium nitrite and sodium thiosulfate are proposed to have an additive effect in the treatment of cyanide poisoning. Specific studies to evaluate such interactions were not completed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No new studies were submitted by the sponsor.

2.6.4.2 Methods of Analysis

No new studies were submitted; therefore, this section is not applicable.

2.6.4.3 Absorption

Sodium thiosulfate and sodium nitrite are administered intravenously and therefore have 100% bioavailability.

2.6.4.4 Distribution

No information provided by the sponsor.

2.6.4.5 Metabolism

No new information was provided by the sponsor.

2.6.4.6 Excretion

No new information was provided by the sponsor.

2.6.4.7 Pharmacokinetic drug interactions

No data provided.

2.6.4.8 Other Pharmacokinetic Studies

No data provided.

2.6.4.9 Discussion and Conclusions

No new information was provided by the sponsor. The Agency has previously approved sodium thiosulfate in conjunction with sodium nitrite for this indication in 1992.

2.6.4.10 Tables and figures to include comparative TK summary

Not provided by sponsor.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided by sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: There were no GLP toxicology studies submitted in support of this NDA application.

Genetic toxicology: Reports in the published literature suggest that sodium nitrite is both genotoxic and clastogenic. Limited data exists on the potential genetic toxicity of sodium thiosulfate, as summarized in the table below:

Standard Battery Genotoxicity (ICH S2b)	**Sodium nitrite**	**Sodium thiosulfate**
In vitro mutagenicity	**Positive**	**Negative**
In vitro mammalian chromosomal damage	**Positive**	No data
In vivo mammalian chromosomal damage	**Positive**	No data

Carcinogenicity: No long-term studies in animals have been conducted to determine the carcinogenic potential of sodium thiosulfate. Carcinogenicity testing of sodium nitrite has been conducted by NTP following nomination by the FDA. Given the acute use of these drugs as an antidote, carcinogenicity studies are not required for this indication.

Reproductive toxicology: The information on sodium thiosulfate and sodium nitrite from the approved 1992 sodium thiosulfate label should be updated to include the known effects of these two drugs on these parameters. The following table briefly summarizes the existing information from the published literature.

Standard Battery Reproductive and Developmental Toxicology Studies	**Sodium nitrite**	**Sodium thiosulfate**
Fertility	No effects noted	No data
Embryo-fetal Development	No clear evidence of teratogenicity but embryotoxic	No clear evidence of teratogenicity but embryotoxic
Prenatal and Postnatal Development	Potential adverse developmental effects	No data

Based on the existing data suggesting embryotoxicity and/or the lack of animal data for the approved components of the kit, the drug product should be considered a Pregnancy Category C.

Special toxicology: None submitted.

2.6.6.2 Single-dose toxicity

No GLP single-dose toxicology studies were submitted for any of the components of the Cyanide Antidote Set, nor were studies with the drug combination completed.

2.6.6.3 Repeat-dose toxicity

No GLP repeat-dose toxicology studies were submitted for any of the components of the Cyanide Antidote Set, nor were studies with the drug combination completed.

2.6.6.4 Genetic toxicology

Studies on the genetic toxicology of both components of the kit are briefly discussed below. Note that a genetic toxicology study was submitted for Sodium Nitrite in support of this NDA.

Sodium Nitrite

Studies published in the literature.

According to the Sponsor's application, "Sodium nitrite is listed as a non-carcinogen, but was giving a positive result in the Ames Test, by the International Agency for Research on Cancer (Kuroki, 1980)."

As part of the review associated with updating the labeling for sodium thiosulfate use only in conjunction with sodium nitrite for cyanide poisoning, publicly available databases were searched by this reviewer. The results of this search were summarized for the proposed labeling. Specifically, the CCRIS and GeneTox databases lists the following genetic toxicology study results for sodium nitrite reported in the literature:

Sodium nitrite has been reported to test **positive** in the bacterial reverse mutation assay (Ames assay) using *S. typhimurium* strains TA100 (± S9 metabolic activation), TA1530 (± S9 metabolic activation), and TA1535 in the absence of metabolic activation (McCann, et al., 1975;Brams, et al., 1987;Zeiger, et al., 1992;Balimandawa, et al., 1994;National Toxicology Program, 2001) and **negative** in *S. typhimurium* strains TA97, TA98, TA102, YG1024, DJ400, DJ460 (± S9 metabolic activation) and TA100 (only without metabolic activation) (Brams, et al., 1987;Zeiger, et al., 1992;Balimandawa, et al., 1994;National Toxicology Program, 2001).

Sodium nitrite has been reported to test **negative** in the mouse lymphoma assay in the absence of metabolic activation (Wangenheim and Bolcsfoldi, 1988).

According to the GeneTox database, sodium nitrite has also been reported in the literature to test **positive** as a clastogen both in vitro and in vivo (Inoue, et al., 1985;Tucker, et al., 1993;Preston, et al., 1981).

Study submitted by the Sponsor.

In Vitro Chromosomal Aberration Assays in Mammalian Cells

Study title: In Vitro Mammalian Chromosome Aberration Test

Study no.:	AB39MP.341.BTL
Conducting laboratory and location:	(b) (4)
Date of study initiation:	14 November 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sodium Nitrate, QB005E5, 100.3%

Key Study Findings

Sodium Nitrate was not deemed clastogenic in human peripheral blood lymphocytes.

Methods

Cell line:	Human Peripheral Blood Lymphocytes
Concentrations in definitive study:	25, 50, 100, 150, 200, 225, 250 mcg/mL
Basis of concentration selection:	The highest concentration was selected based on its ability to produce ≥ 50% reduction in the mitotic index relative to solvent control, with a sufficient number of scorable metaphase cells. Several lower concentrations were included in the evaluation.
Negative control:	Water (CAS No.: 7732-18-5; (b) (4) (b) (4)
Positive control:	Mitomycin C (MMC; CAS No.: 50-07-7) served as a control in the non-activated test system. Cyclophosphamide (CP; CAS No.: 6055-19-2) served as a control in the S9-activated test system.
Formulation/Vehicle:	(b) (4) Water (CAS No.: 7732-18-5; (b) (4) (b) (4)
Incubation & sampling time:	The **incubation time** was 44-48 hours. The sampling time was

Study Validity

Given the standards established in the FDA/CFSAN Redbook guidelines, the study appears to be valid based on the positive controls employed; type and number of cells evaluated; methods to count and evaluate chromatid- and chromosome-type aberrations

and to select test article concentrations used; test assay conditions maintained; and definition of a positive responses measured.

Results

The Sponsor reported that at 250 mcg/mL of Sodium Nitrate the mitotic index was 53-56%, relative to control, across the test systems employed. Note that none of the test article doses produced statistically significant increases in the percentage of cells with structural or numerical aberrations when compared to the solvent control.

Sodium Thiosulfate

The sponsor did not identify any studies testing the mutagenic potential of sodium thiosulfate. However, a study published by the U.S. Food and Drug Administration reports that sodium thiosulfate pentahydrate tested **negative** for mutagenic potential in the bacterial reverse mutation assay (Ames test) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 (± S9 metabolic activation) (Prival, et al., 1991).

Although not considered part of the standard battery of modern genetic toxicology studies, the U.S. EPA reported that sodium thiosulfate did not produce chromosome aberrations in the common onion (*Allium cepa*) (Grant, 1982).

To the best of this reviewer's knowledge, there are no in vitro or in vivo assays reported to assess the potential for sodium thiosulfate to produce DNA damage in mammalian cells.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were submitted in support of this NDA. Carcinogenicity studies are not typically required for an acute indication. However, since data in the published literature exists regarding the potential carcinogenicity of components of the proposed kit, the existing information should be included in the product labeling.

Sodium Nitrite

The National Toxicology Program (NTP) has tested the carcinogenic potential of sodium nitrite via the oral route of in the rat and mouse model (National Toxicology Program, 2001), since sodium nitrite is used as a color fixative and preservative in meats and fish. The Food and Drug Administration nominated sodium nitrite to the NTP for toxicity and carcinogenicity studies based on its widespread use in foods. Male and Female F344/N rats and B6C3F1 mice were exposed to sodium nitrite (99% pure) in drinking water for 2 years. The summary of the NTP studies are reproduced below:

> **2-YEAR STUDY IN RATS**
> Groups of 50 male and 50 female rats were exposed to 0, 750, 1,500, or 3,000 ppm sodium nitrite (equivalent to average daily doses of approximately 35, 70, or 130 mg/kg to males and 40, 80, or 150 mg/kg to females) in drinking water for 2 years. For toxicokinetic studies of plasma nitrite and blood methemoglobin, 10 male and 10 female special study rats were exposed to the same concentrations for 12 months. Survival of exposed groups was similar to that of the controls. Mean body weights of males and females exposed to 3,000 ppm were less than those of the controls throughout the study. Water consumption by males and females exposed to 3,000 ppm was less than that by the controls throughout the study, and that by the other exposed groups was generally less after week 14. The incidences of hyperplasia of the forestomach epithelium in males and females exposed to 3,000 ppm were significantly greater than those in the control groups. The incidence of fibroadenoma of the mammary gland was significantly

> increased in females exposed to 1,500 ppm, and the incidences of multiple fibroadenoma were increased in 750 ppm and 1,500 ppm females; however, these neoplasms occur with a high background incidence, and no increase was seen in the 3,000 ppm group. The incidences of mononuclear cell leukemia were significantly decreased in males and females exposed to 1,500 or 3,000 ppm.
>
> **2-YEAR STUDY IN MICE**
> Groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 750, 1,500, or 3,000 ppm sodium nitrite (equivalent to average daily doses of approximately 60, 120, or 220 mg/kg to males and 45, 90, or 165 mg/kg to females) in drinking water for 2 years. Survival of exposed groups was similar to that of the controls; mean body weights of 3,000 ppm females were less than those of the controls throughout the study. Exposed groups generally consumed less water than the control groups.
>
> The incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice occurred with a positive trend. The incidence of hyperplasia of the glandular stomach epithelium was significantly greater in 3,000 ppm males than in the controls.

As these studies are well controlled studies conducted by the U.S. Government, the results should be described in the product labeling.

Sodium Thiosulfate

There are no long-term animal studies to evaluate the carcinogenic potential of sodium thiosulfate. Given the acute life-threatening indication, carcinogenicity studies are not deemed necessary.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Clinical studies to evaluate the potential effects of sodium nitrite or sodium thiosulfate on fertility of either males or females have not been reported.

Sodium Nitrite

No information was provided by the sponsor of this NDA.

Multigenerational fertility and reproduction studies conducted by the National Toxicology Program did not detect any evidence of an effect of sodium nitrite (0.0, 0.06, 0.12, and 0.24% weight/volume) on either fertility or any reproductive parameter in Swiss CD-1 mice. This treatment protocol resulted in approximate doses of 125, 260, and 425 mg/kg/day (National Toxicology Program, 1997). The highest exposure in this mouse study is 4.6 times greater than the highest clinical dose of sodium nitrite that would be used to treat cyanide poisoning (based on a body surface area comparison).

Sodium Thiosulfate

There are no preclinical studies examining the effects of sodium thiosulfate on fertility.

Embryofetal development

Sodium Nitrite

The sponsor provided the following comments regarding the potential reproductive and developmental toxicity of sodium nitrite:

> In pregnant rats, the administration of sodium nitrite at doses of 2.5 mg/kg and 30 mg/kg, no other fetal effects were reported other than methemoglobin induction. [Sponsor reference: (Gruener, et al., 1973)]
>
> Sodium nitrite doses of 100 mg/kg were teratogenic in rats. Cyanosis was observed in 25% of newborn rats at birth following maternal administration of sodium nitrite (100 mg/kg) and in 6% of new born rats with a maternal dose of 5 mg/kg. [Sponsor reference: (Izmerov, 1982)]
>
> As sodium nitrite is only likely to be administered once, or at most a few times, as an antidote, the main concern would appear to be induction of fetal methemoglobinaemia if administered to a pregnant patient. The risk to fetus from maternal cyanide poisoning would seem to override the risk from possible fetal methemoglobin induction. [Sponsor reference: (Padberg and Martin, 1939)]

The information in the cited Izmerov review is difficult to interpret due to poor quality of duplication and the fact that the review summarized findings from studies reported at a symposium. The copies of the referenced studies were not available for more detailed review. Due to the lack of adequate details of the study, they are not recommended for inclusion in the label.

Based upon a review of the literature by this reviewer, the following information regarding the teratogenic potential of this compound was obtained.

The potential reproductive toxicity of sodium nitrite exposure restricted to the prenatal period has been reported in guinea pigs, mice, and rats. There was no evidence of teratogenicity in either guinea pigs, mice, or rats (Khera, 1982;Roth, et al., 1987;Globus and Samuel, 1978;Shimada, 1989;Sleight, et al., 1972;Druckrey, et al., 1963;National Toxicology Program, 1997;National Toxicology Program, 2001). However, sodium nitrite treatment of pregnant guinea pigs with 60 or 70 mg/kg/day resulted in abortion of the litters within 1-4 days of treatment (Sinha and Sleight, 1971). All animals treated with 70 mg/kg, s.c., sodium nitrite died within 60 minutes of treatment. Further studies demonstrated that a dose of 60 mg/kg resulted in measurable blood levels of methemoglobin in the dams and their fetuses for up to 6 hours post treatment. Maternal methemoglobin levels were higher than the levels in the offspring at all times measured.

Based on a body surface area comparison, a 60 mg/kg dose in the guinea pig that resulted in death was only 1.7 times higher than the highest clinical dose of sodium nitrite that would be used to treat cyanide poisoning (based on a body surface area comparison).

Sodium Thiosulfate

In animal studies, there are no teratogenic effects in offspring of hamsters treated during pregnancy with sodium thiosulfate in doses similar to those given intravenously to treat cyanide poisoning in humans (Willhite, 1983). Other studies suggest that treatment with sodium thiosulfate ameliorates the teratogenic effects of maternal cyanide poisoning in hamsters (Doherty, et al., 1982;Willhite, 1983). In other studies, sodium thiosulfate was not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day, respectively (Food and Drug Research Labs, 1972;Food and Drug Research Labs, 1974).

Prenatal and postnatal development

Sodium Nitrite

Behavioral and neurodevelopmental studies in rats suggest persistent effects of prenatal exposure to sodium nitrite that were detectable postnatally. Specifically, animals that were exposed prenatally to sodium nitrite demonstrated impaired discrimination learning behavior (both auditory and visual) and reduced long-term retention of the passive-avoidance response compared to control animals (Nyakas, et al., 1990). Additional studies demonstrated a delay in the development of AchE and 5-HT positive fiber ingrowth into the hippocampal dentate gyrus and parietal neocortex during the first week of life of prenatal nitrite treated pups. These changes have been attributed to prenatal hypoxia following nitrite exposure (Nyakas, et al., 1994).

In studies conducted with Long-Evans rats, sodium nitrite administered in drinking water during pregnancy and lactation resulted in severe anemia, reduced growth and increased mortality in the offspring (Roth, et al., 1987;Roth and Smith, 1988).

Sodium Thiosulfate

No studies on the effects of sodium thiosulfate on prenatal and postnatal development were identified by the sponsor.

2.6.6.7 Local tolerance

No studies were submitted to evaluate the local toxicity of sodium thiosulfate, or sodium nitrite.

2.6.6.8 Special toxicology studies

No studies were submitted.

2.6.6.9 Discussion and Conclusions

See overall conclusions and recommendations below.

2.6.6.10 Tables and Figures

None submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None submitted by sponsor.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This NDA proposes the use of the two drug combination of sodium nitrite and sodium thiosulfate for the treatment of cyanide poisoning. The Agency has previously approved the use of sodium thiosulfate, in conjunction with sodium nitrite, as an antidote in the treatment of cyanide poisoning in 1992. The Sponsor is referencing the Agency's previous findings for these two drugs. Based on the specifications reviewed and justifications discussed above, NDA 201-444 is deemed a complete response and can not be recommended for approval.

Unresolved toxicology issues (if any):
See executive summary.

Recommendations: From the nonclinical pharmacology and toxicology perspective, NDA 201-444 is considered complete; however, it can not be approved, from the pharmacology/toxicology perspective.

Suggested labeling: See the executive summary for preliminary recommended changes to the label at this time.

R. Daniel Mellon, Ph.D. (Pharmacology Toxicology Supervisor) and
Marcus S. Delatte, Ph.D. (Pharmacology Toxicology Reviewer)
DAAP/ODE2/OND/CDER/FDA

APPENDIX/ATTACHMENTS

Reference List

Balimandawa M, De MC and Leonard A (1994) The mutagenicity of nitrite in the Salmonella/microsome test system. *Mutat Res* **321**:7-11.

Bhutia YD, Gautam A, Jain N, Ahmed F, Sharma M, Singh R, Kumar S, Mendki MJ, Kumar P and Vijayaraghavan R (2010) Acute and sub-acute toxicity of an insect pheromone, N-heneicosane and combination with insect growth regulator, diflubenzuron, for establishing no observed adverse effect level (NOAEL). *Indian Journal of Experimental Biology* **48**:744-751.

(b) (4)

(b) (4)

(b) (4)

Brams A, Buchet JP, Crutzen-Fayt MC, De MC, Lauwerys R and Leonard A (1987) A comparative study, with 40 chemicals, of the efficiency of the Salmonella assay and the SOS chromotest (kit procedure). *Toxicol Lett* **38**:123-133.

(b) (4)

(b) (4)

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/s/

MARCUS S DELATTE
11/04/2010

RICHARD D MELLON
11/04/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 201444 **Applicant: Hope Pharma** **Stamp Date: May 21, 2010**

Drug Name: (b) (4) **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing: Filable

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A, no toxicology studies were required.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A, no toxicology studies were required.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A, no toxicology studies were required.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			The referenced justification for DP spec for nitrate can not be located in submission, this can be clarified and is not deemed a filing issue. See comment below for 74-day letter.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			The only exception to date appears to be nitrate, but this will not be deemed a filing issue.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

At the filing meeting, the CMC review team noted that the NDA contains an extractable study for the (b) (4) stoppers that has identified numerous extractables. Leachable data was not provided, therefore, the worse case scenario will have to assume all extractables are released into the drug product. There does not appear to be any toxicological risk assessment of these extractables.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Submit a toxicological risk assessment for the maximum daily exposure to each identified extractable from the (b) (4) stoppers noted in (b) (4) (b) (4) as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." In general, the evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known

genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

2. Although discussed in the submission, we are not able to locate the justification for the proposed drug product specification for nitrate, which exceeds the ICHQ3B(R2) qualification threshold of NMT (b) (4) Please identify where in the submission this discussion is located or provide rationale for the safety of the proposed specification.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201444	ORIG-1	HOPE PHARMACEUTICALS	SODIUM NITRITE INJECTION

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/s/

RICHARD D MELLON
07/15/2010