CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults**

From: David J. Lee, Ph.D.	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

DATE: 11/15/10	NDA 201444	Serial -	DATE OF DOCUMENT: 5/21/10

DRUG NAME Nithiodote Injection, USP (Sodium nitrite and sodium thiosulfate)	Date of informal/Formal Consult:

NAME OF THE SPONSOR: [Hope Pharmaceticals]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ PHASE IV RELATED	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ DISSOLUTION/IN-VITRO RELEASE	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ BIOAVAILABILITY STUDIES	☐ CORRESPONDENCE
☐ PROTOCOL	☐ IN-VIVO WAIVER REQUEST	☐ DRUG ADVERTISING
☐ SAFETY PROTOCOL	☐ SUPAC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ANNUAL REPORTS
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ FAX SUBMISSION
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☒ OTHER *(SPECIFY BELOW):*
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	[Memo to the NDA file]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Hope Pharmaceuticals has submitted NDA 201444 in accordance with 505(b)(2) provisions of the Food, Drug and Cosmetic Act for the use of Nithiodote for treatment of (b) (4) cyanide poisoning. Nithiodote is a cyanide antidote kit containing co-packaged sodium thiosulfate injection and sodium nitrite injection. The sponsor requested priority review for Nithiodote and has been granted the priority status. The request was based on the 'need for additional antidotes against cyanide toxicity (especially in light of the potential for use of cyanide by terrorists or use of cyanide against our military personnel in the battlefield)', 'there are no FDA-approved sodium nitrite and sodium thiosulfate products currently marketed in the United States', and, 'antidote kit

has specific drug administration recommendations for pediatric patients'.

The sponsor is relying on the Agency's previous findings of safety and effectiveness of NDA 20-166. During a pre-IND meeting held on July 27, 2007, the sponsor was informed that a 505(b)(2) application may rely for approval on published literature and/or upon the Agency's finding of safety and effectiveness for an approved product, to the extent such reliance is scientifically appropriate, and that the NDA application needs to contain adequate CMC information. Further, the sponsor may rely on the Agency's finding of safety and effectiveness for a previously approved product, NDA 20-166, for the cyanide poisoning (a sodium thiosulfate injection, for use in combination with sodium nitrite injection), although this product is listed in the discontinued drug product section of the Orange Book. Additionally, the sponsor can utilize published literature to address other requirements for a NDA. During the same meeting, the sponsor was informed that the sponsor would not require additional toxicological, pharmacokinetic or clinical information to support the safety and efficacy for Nithiodote (Pre-IND Meeting Minutes dated August 8, 2007).

As agreed in the Pre-IND meeting, this NDA did not contain any clinical pharmacology/pharmacokinetic or clinical studies, and literature review of publicly available clinical data regarding the clinical safety and efficacy of sodium thiosulfate and sodium nitrite. The sponsor included a biowaiver request for the bioavailability/bioequivalence requirement. Included in the reasons for requesting a waiver is the Agency's position conveyed in the August 2007 Pre-IND meeting that the NDA applications for cyanide antidotes involving the administration of sodium nitrite and sodium thiosulfate injections in a manner consistent with the approved sodium thiosulfate labeling do not require additional pharmacokinetic studies. The sponsor submitted some literature articles pertaining to pharmacokinetics and pharmacodynamics of sodium nitrite and sodium thiosulfate. Upon the cursory review of the submitted information, it is concluded that information described in the literature articles does not significantly contribute to the understanding of clinical pharmacology aspects of the product than what is already known to the Agency or have any impact on the label. It is also noted that the sponsor's labeling contains same information from the NDA 20-166, and thus there are no issues with the submitted label from the clinical pharmacology perspective.

Overall, NDA 201444 is acceptable from a clinical pharmacology perspective.

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/s/

DAVID J LEE
11/15/2010

SURESH DODDAPANENI
11/15/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**201-444/S-000**
Submission Date:	5/21/10
Generic Name:	(b) (4)
Formulation:	Copackged injection
Strength:	250/mL and /30mg/mL
Applicant:	Hope Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Biowaiver request

The proposed drug product by the applicant is a cyanide antidote kit consisting of co-packaged sodium nitrite injection and sodium thiosulfate injection for the treatment of cyanide poisoning. The reference listed drug (RLD) is Sodium Thiosulfate Injection, USP (NDA 20-166), which was approved in combination with sodium nitrite injection for the treatment of cyanide poisoning. The applicant requests a waiver per 21 CFR 314.90 for the bioavailability/bioequivalence requirement.

COMMENTS

It is justified to grant a waiver for the in vivo bioavailability of sodium hiosulfate and sodium nitrite based on the following considerations:

1. The Agency previously agreed that NDA applications for cyanide antidotes involving the administration of sodium nitrite injection and sodium thiosulfate injection in a manner consistent with the approved sodium thiosulfate labeling do not require additional pharmacokinetic studies;
2. The bioavailability is self evident for the intravenously administered sodium thiosulfate injection and sodium nitrite injection per 21 CFR 320.22. The minor differences in the inactive ingredients may not affect the bioavailability.

RECOMMENDATION

The biowaiver can be granted.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 201-444
Angelica Dorantes, Patrick Marroum, John Duan

APPENDIX. The Biowaiver Request

The applicant requests a waiver per 21 CFR 314.90 for the bioavailability/bioequivalence requirement described in FDA's Guidance for Industry "Applications Covered by Section 505(b)(2)"

The proposed drug product being developed by the applicant is a cyanide antidote kit consisting of co-packaged sodium nitrite injection and sodium thiosulfate injection for the treatment of cyanide poisoning. The reference listed drug (RLD) is Sodium Thiosulfate Injection, USP (NDA 20-166), which was approved in combination with sodium nitrite injection for the treatment of cyanide poisoning.

The NDA for the applicant's cyanide antidote kit is submitted in accordance with 505(b)(2) of the Food, Drug and Cosmetic Act. The NDA intends to rely on the FDA's previous findings of safety and efficacy for sodium thiosulfate injection in combination with sodium nitrite injection for the treatment of cyanide poisoning, as described in NDA 20-166.

The applicant had a pre-NDA meeting on July 27, 2007 with FDA DAARP for the applicant's cyanide antidote kit. The Agency encouraged the submission of an NDA for co-packaged sodium nitrite and sodium thiosulfate drug products for the treatment of cyanide poisoning, and would not require further documentation of the safety or efficacy of the use of sodium nitrite and sodium thiosulfate for the treatment of cyanide poisoning, but would require a complete CMC section. The applicant received the following guidance from the Agency:

"Additional comments regarding the biopharm, pharm-tox and clinical questions: Internal discussions at FDA have led us to conclude that the risk-benefit analysis which led to the approval of sodium thiosulfate included the use of sodium nitrite. Therefore, applications involving the administration of these two products to treat cyanide poisoning in a manner consistent with the approved sodium thiosulfate label do not require additional toxicological, pharmacokinetic or clinical information to support the safety or efficacy of this combination of antidotes. Approval of such applications will depend on the adequacy of the Chemistry, Manufacturing and Controls Information submitted and the related inspections."

FDA has informed the applicant that no additional pharmacokinetic information is necessary to support an NDA for sodium thiosulfate and sodium nitrite as an antidote for cyanide poisoning. This waiver of the BA/BE requirement is being requested to ensure compliance with the FDA guidance on 505(b)(2) applications.

The proposed cyanide antidote kit is indicated for the treatment of (b) (4) cyanide poisoning. The cyanide antidote kit is administered intravenously. The proposed dosage regimen to treat cyanide poisoning is as follows:

1. Inject intravenously 10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute. The recommended dose of a 3% solution of sodium nitrite for children is 6 to 8 mL/m^2 of body surface area (approximately 0.2 mL/kg of body weight) but is not to exceed 10 mL of a 3% solution (300 mg).

2. Immediately thereafter, inject 50 mL of a 25% solution (12.5 g) of sodium thiosulfate for adults. The recommended dose of a 25% solution of sodium thiosulfate for children is 30 to 40 mL/m^2 of body surface area (approximately 1.0 mL/kg of body weight); but dosage should not exceed 50 mL of a 25% solution (12.5 g). The same needle and vein may be used.

The above proposed dosage regimen for the cyanide antidote kit is identical to the prescribing information from the approved package insert for Sodium Thiosulfate Injection, USP NDA 20-166 (dated February 18, 1992).

Sodium thiosulfate injection, the reference listed drug (RLD), is listed in the discontinued product section of FDA Orange Book for sodium thiosulfate. Sodium Thiosulfate Injection, USP (NDA 20-166) was developed by the US Army and was approved in February 14, 1992. The FDA's approval of the US Army's NDA for sodium thiosulfate injection was for use in combination with a sodium nitrite injection for the treatment of cyanide poisoning.

The US Army has discontinued marketing sodium thiosulfate. Thus the sodium thiosulfate injection drug product is no longer commercially available.

The sodium thiosulfate part of the Cyanide Antidote Kit is a 50 mL glass vial of sodium thiosulfate injection 250 mg/mL (containing 12.5 grams of sodium thiosulfate).

The sodium thiosulfate injection drug product in the cyanide antidote kit is 1) a parenteral solution intended solely for administration by injection and 2) contains the same active ingredient in the same concentration, and 3) contains the same inactive ingredients at nearly the same concentrations as in the sodium thiosulfate drug product described in NDA 20-166, and thus the two drug products are essentially similar. Table 1 shows the formulation of the sodium thiosulfate injection packaged in the cyanide antidote kit.

Table 1: Formulation of Sodium Thiosulfate Injection in Cyanide Antidote Kit

Ingredient	Proposed Formulation	Approved Formulation
Sodium thiosulfate pentahydrate, USP		(b) (4)
Potassium chloride, USP		
Boric acid, NF		
Boric acid, NF		
Sodium hydroxide, NF		
(b) (4) USP		

The sodium nitrite part of the cyanide antidote kit is a 10 mL glass vial of sodium nitrite injection 30 mg/mL (containing 300 mg of sodium nitrite). It contains the same active and inactive ingredients in the same concentrations as in the sodium nitrite injection drug

products that were commercially available and used in conjunction with the RLD sodium thiosulfate injection.

The prescribing information from the approved NDA 20-166 states, "Inject intravenously 10 mL of a 3% solution (300 mg) of sodium nitrite at a rate of 2.5 to 5 mL/minute. The recommended dose of a 3% solution of sodium nitrite for children is 6 to 8 mL/m^2 body surface area (approximately 0.2 mL/kg of body weight) but is not to exceed 10mL of a 3% solution (300 mg) (NOTE: Sodium nitrite is not supplied with this package.)"

The sodium nitrite drug product in the proposed cyanide antidote kit contains the same active ingredient in the same concentration as the sodium nitrite injection drug product described in NDA 20-166, and thus the two drug products are essentially similar. Table 2 shows the formulation of the sodium nitrite injection packaged in the cyanide antidote kit.

Table 2: Formulation of Sodium Nitrite Injection in Cyanide Antidote Kit

Ingredient	Formulation
Sodium nitrite, USP	30.0 mg/mL
(b) (4) USP	(b) (4)

Abbreviations: NF, National Formulary; q.s., quantity sufficient; USP, United States Pharmacopeia; (b) (4)

It is justified to grant a waiver for the in vivo bioavailability of sodium thiosulfate and sodium nitrite based on the following considerations:

1. The Agency previously agreed that NDA applications for cyanide antidotes involving the administration of sodium nitrite injection and sodium thiosulfate injection in a manner consistent with the approved sodium thiosulfate labeling do not require additional pharmacokinetic studies;
2. The RLD sodium thiosulfate injection is currently discontinued;
3. The bioavailability is self evident for the intravenously administered sodium thiosulfate injection and sodium nitrite injection and thus both drugs meet the requirements for a waiver per 21 CFR 320.22. The minor differences in the inactive ingredients may not affect the bioavailability.

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

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/s/

JOHN Z DUAN
07/08/2010

PATRICK J MARROUM
07/08/2010