

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209387Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 209387

Drug: Sodium Nitroprusside (b) (4) Injection

Class: Vasodilator

Applicant: Exela Pharma Sciences, LLC.

Proposed Indications:

1. For the immediate reduction of blood
2. For producing controlled hypotension in order to reduce bleeding during surgery
3. Treatment of acute heart failure to reduce left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, peripheral vascular resistance and mean arterial blood pressure

Date of submission: May 9, 2016

PDUFA date: March 9, 2017

Target Action date: March 8, 2017

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation 1:

Division of Cardiovascular & Renal Product

Division Director: Norman Stockbridge, MD, PhD

Clinical Team Leader: Martin Rose, MD

Clinical reviewer: Fortunato Senatore, MD

Pharmacology/Toxicology Team Leader: Thomas Papoian, PhD

Pharmacology/Toxicology: Rama Dwivedi, PhD

Regulatory Project Manager: Maryam Kord Bacheh Changi, PharmD

Office of Pharmaceutical Quality:

CDTL and Product Quality ATL: Mohan Sapru, PhD

Branch Chief: Wendy Wilson, PhD

Drug substance: Sharon Kelly, PHD

Drug Product: Rao Kambhampati, PhD

Biopharmaceutics: Om Ananad, PhD

Facility: Christina Capacci-Daniel, PhD

Office of Clinical Pharmacology:

Sudharshan Hariharan, PhD

Ju-Ping Lai, PhD

Office of Surveillance and Epidemiology:

DPV: Amy Chen, PharmD

DMEPA: Ashleigh Lowery, PharmD, BCCCP

Office of Prescription Drug Promotion:

Zarna Patel, PharmD

Division of Pediatric and Maternal Health:

Catherine Roca, MD,

III. BACKGROUND

This application for sodium nitroprusside is being submitted by Exela Pharma Sciences, LLC as a 505(b)(2) application. This NDA is a 505(b)(2) with no clinical data as a result no financial disclosure review was needed.

For labeling they are referencing the RLD being relied upon from Hospira ANDA 071961. In response to the Division's 74 day letter comments, the sponsor later on submitted the updated information to reference the RLD to AbbVie's NDA 018450.

There is a pre-IND associated with this application in which the sponsor requested a meeting to discuss the planned NDA. The meeting was cancelled after the preliminary responses were sent. Subsequently, the sponsor sent 2 additional communications requesting advice in order to prepare for the submission. Exela states that the difference between the two products is the inactive ingredients. The new formulation contains 9 mg/mL Sodium Chloride, is unbuffered, preservative free, non pH-adjusting and is ready for direct injection without further diluting unlike the RLD. There is no new clinical data in support of this NDA, only CMC and biopharmaceutics.

IV. APPLICATION REVIEW

1. User Fee

The User fee for this application was paid in full on March 16, 2015. User Fee I.D. Number for this application is PD3015970.

2. Pediatric Review Committee (PeRC):

This NDA does not trigger PREA. The PeRC meeting was not needed.

3. Review Status:

NDA 209387 was considered a Standard Review (10-month clock).

Advisory Committee:

There was no Advisory Committee meeting for this NDA because the application did not raise any significant safety or efficacy issues.

4. Trade name

Per the December 8, 2016 proprietary name submission, Exela has obtained the trademark Nipride. On December 14, 2017 Exela proposes the proprietary name Nipride RTU for sodium nitroprusside 50 mg/100 mL injection, which is ready for intravenous administration without further dilution. The proposed proprietary name is acceptable.

5. Facilities Inspections:

There was no Clinical Inspection required for this application

6. Regulatory Timeline:

PIND Meeting: October 13, 2015 (Cancelled)

NDA Receipt date: May 9, 2016

Filing date: July 8, 2016

74- Day letter: July 22, 2016

Mid-Cycle meeting: October 03, 2016

Proprietary name accepted: March 2, 2017 (Review), March 7, 2017(Letter)

Advisory committee: N/A

PDUFA Date: March 9, 2017

Approval letter: March 8, 2017

7. Reviews

a) Divisional Memorandum

Dr. Stockbridge's memo documented his concurrence with the review team's recommendation to approve this new drug application. Please refer to his memo for further details.

b) Cross-Discipline Team Leader Review

Dr. Sapru recommended approval for NDA 209387. All the reviews of this application recommended approval, and he concurs with the reviewers. Based on the CMC review, an expiry period of 12 months is granted for Sodium Nitroprusside in 0.9% Sodium Chloride Injection when stored at 20° to 25°C (68° to 77°F) using the applicant's proposed container/closure system.

c) Clinical Pharmacology Review

No Separate Review was needed

d) Pharmacology & Toxicology Review

No Separate Review was needed

e) Office of Pharmaceutical Quality Review- February 28, 2017

An integrated summary was written by Dr. Sapru for product quality. Approval is recommended from the quality perspective.

8. Consults

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: 01/31/2017; 03/02/2017
- OPDP: 01/31/2017
- Patient Labeling (Instructions for Use): N/A
- DPMH: 01/12/2017

9. Labeling

Labeling discussions occurred with the applicant. The final agreed-upon labeling will be attached to the approval letter.

V. CONCLUSION:

After considering all primary and consult reviews, the Division issued an Approval recommendation for NDA 209387 on March 7, 2017.

The Approval Letter was signed by Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products on March 8, 2017.

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/s/

MARYAM K CHANGI
03/08/2017



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 209387 Nitroprusside (Nipride RTU) for hypertensive crisis, control of surgical bleeding, and heart failure.

Sponsor: Exela Pharma Sciences

Review date: 7 March 2017

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's decision to approve this application.

This application has been the subject of reviews of CMC (Kelly, Kambhampati, Janoria, Chen, Anand, Capacci-Daniel, & Sapru; 28 February 2017). There is also a CDTL memo (Sapru; 1 March 2017), with which I am in complete agreement.

This is a 505(b)(2) application relying upon safety and effectiveness of RLD Nitropress. There are no remaining product quality issues; the amber vials of 50 mg in 100 mL of 0.9% sodium chloride have an expiry date of 12 months. The facility inspections are complete.

There are no new nonclinical, BA/BE, or clinical studies.

Labeling negotiations are complete. Labeling was updated to PLR/PLLR with numerous modernizations. The indications were not altered.

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/s/

NORMAN L STOCKBRIDGE
03/07/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209387	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/A Established/Proper Name: sodium nitroprusside Dosage Form: (b) (4) Injection Strengths: 0.5mg/mL (50 mg/ 100 mL)		
Applicant: Exela Pharma Sciences, LLC.		
Date of Receipt: May 9, 2016		
PDUFA Goal Date: March 9, 2017		Action Goal Date (if different): March 8, 2017
RPM: Maryam Changi		
Proposed Indication(s): <ul style="list-style-type: none">• For the immediate reduction of blood pressure of adult and pediatric patients in hypertensive crises.• For producing controlled hypotension in order to reduce bleeding during surgery.• For the treatment of acute (b) (4) heart failure		

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 018450, NITROPRESS Injection,	Exela is relying on RLD for Labeling. Please note that NDA 018450 has been Discontinued by Abbvie, Inc. The Agency has previously determined that the discontinuation was for reasons unrelated to safety or efficacy of the drug product.

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The Applicant requested a waiver of *in vivo* Bioavailability/Bioequivalence requirements for Exela's Sodium Nitroprusside (b) (4) Injection.

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (sodium nitroprusside), and has the same dosage form, route of administration and indication as the LD. However, the proposed product and the listed drug product are different with regard to the inactive ingredients [sodium chloride vs. dextrose] and the concentration of the active ingredient.

As supported by the additional information [pH, osmolality and literature], the differences in inactive ingredients and the difference in the concentration of the active ingredient are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via IV infusion route.

The Applicant provided literature information supporting their claim that the human pharmacokinetics and pharmacodynamics show that the disposition of the sodium nitroprusside is rapid and are not influenced by variations in dosing rates over a wide range. The Applicant reported that several clinical studies reported in the literature have used sodium nitroprusside infusion solutions prepared with normal saline and not with dextrose as recommended in the LD labeling. The slight differences in the pH and osmolality and the differences in the amounts of sodium chloride and dextrose are not likely to affect the disposition of sodium nitroprusside; therefore these differences are acceptable.

Specifically for NDA 209387, the differences in inactive ingredients are not expected to have an impact on the disposition of sodium nitroprusside from the Applicant's proposed formulation as compared to the reference formulation.

Because the initial (0.3 mcg/kg/min), average (3 µg/kg/min) and maximal (10 mcg/kg/min) dosing of sodium nitroprusside remains the same from the Applicant's proposed formulation and the reference formulation, therefore, the difference in the administered volume and infusion rate, to compensate for the difference in the concentration of the active ingredient, are not expected to affect the BA/BE, safety and efficacy of the proposed drug product.

Overall, the differences in the active ingredients, concentration of the active ingredient, and the differences in the volume and infusion rate are not expected to cause a difference in the the BA/BE, safety and efficacy between the listed and the proposed drug product. Therefore, a bridge between the proposed drug product and the listed drug product has been established (21 CFR 320.24(b)(6)).

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 as labeled 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).
Vasotec (enalapril maleate) tablets*

- (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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Nitropress Injection	018450	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 final OTC drug monograph?

YES NO

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

Name of drug(s) described in a final OTC drug 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:

NITROPRESS 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 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").

This application provides for a change in formulation.

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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

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?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

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

*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)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
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): Nitropress® Injection – NDA 018450

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*

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 and 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):

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):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (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

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/s/

MARYAM K CHANGI

03/08/2017

505(b)(2) was cleared on 02/28/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: January 31, 2017

To: Maryam Kord Bacheh Changi
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Sodium Nitroprusside in 0.9% Sodium Chloride Injection, for intravenous use**
NDA: 208036
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on June 13, 2016, for Sodium Nitroprusside in 0.9% Sodium Chloride Injection, for intravenous use. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI. Our comments are based on the proposed labeling uploaded on Sharepoint on January 23, 2017. OPDP only has one comment in section 5.5.

Carton and Container Label

OPDP reviewed the Carton and Container Labeling submitted by the sponsor on January 19, 2017 and provided the following comments to DCRP via email on January 24, 2017:

- The proposed labeling includes information related to the serious risk of decrease in blood pressure associated with the drug (b) (4). This presentation is misleading because it minimizes the risks associated with the product. Specifically, by only including information related to the risk of decreased blood pressure, it suggests that this is the only risk associated with the drug, when such is not the case. We recommend either (b) (4)

We note that the revised Carton & Container labeling was submitted by the sponsor on January 27, 2017, [REDACTED] ^{(b) (4)}.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the proposed labeling, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

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/s/

ZARNA PATEL
01/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 31, 2017
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 209387
Product Name and Strength: Sodium nitroprusside injection, 50 mg/100 mL (0.5 mg/mL)
Submission Date: January 27, 2017
Applicant/Sponsor Name: Exela Pharma Sciences
OSE RCM #: 2016-1372-2
DMEPA Primary Reviewer: Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Sodium Nitroprusside injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memo.^{a,b} The application currently has a proposed proprietary name under review, so labels and labeling were submitted both with and without the proprietary name.

2 CONCLUSION

The revised Sodium Nitroprusside injection container label and carton labeling are acceptable from a medication error perspective. We note the proposed proprietary name Nipride RTU is still under review. The label and labeling with the proprietary name are acceptable only after the name is found acceptable. We have no further recommendations at this time.

^a Lowery A. Label and Labeling Review for Sodium nitroprusside injection (NDA 209387). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 18. OSE RCM No.: 2016-1372.

^b Lowery A. Label and Labeling Memo for Sodium nitroprusside injection (NDA 209387). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Jan 25. OSE RCM No.: 2016-1372-1.

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/s/

ASHLEIGH V LOWERY
01/31/2017

CHI-MING TU
01/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 25, 2017
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 209387
Product Name and Strength: Sodium nitroprusside injection, 50 mg/100 mL (0.5 mg/mL)
Submission Date: January 19, 2017
Applicant/Sponsor Name: Exela Pharma Sciences
OSE RCM #: 2016-1372-1
DMEPA Primary Reviewer: Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Sodium nitroprusside injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a The application currently has a proposed proprietary name under review, so labels and labeling were submitted both with and without the proprietary name.

2 CONCLUSION

The revised container label and carton labeling may be further improved from a medication error perspective.

The presentation of the proprietary name (Nipride – RTU) on the revised container label and carton labeling does not reflect the currently proposed proprietary name (Nipride RTU). In addition, as stated in our previous review, the carton labeling does not include a lot number

^a Lowery A. Label and Labeling Review for Sodium nitroprusside injection (NDA 209387). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 18. OSE RCM No.: 2016-1372.

and expiration date as required by 21 CFR 201.10(i)(1) and 21 CFR 201.17. We provide recommendations in Section 3 below.

3 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES

We note the proposed proprietary name Nipride RTU is still under review. The labels and labeling with the proprietary name are acceptable only after the name is found acceptable.

We recommend the following be implemented prior to approval of this NDA:

- A. General Comments (Container labels and carton labeling)
 - 1. Revise the container label and carton labeling presented with the proprietary name to reflect the proposed proprietary name. The proposed proprietary name currently under review is Nipride RTU (without the dash).
- B. Carton Labeling
 - 1. Revise the carton labeling to include the lot number and expiration date. The lot number is required per 21 CFR 201.10(i), and the expiration date per 21 CFR 201.17.

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

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/s/

ASHLEIGH V LOWERY
01/25/2017

CHI-MING TU
01/25/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209387

Application Type: New NDA

Drug Name(s)/Dosage Form(s): sodium nitroprusside (b) (4) Injection

Applicant: Exela Pharma Sciences, LLC

Receipt Date: May 9, 2016

Goal Date: March 9, 2017

SRPI Completion Date: 07/07/2016

1. Regulatory History and Applicant's Main Proposals

This application was received on May 9, 2016. It is a 505(b)(2) application. Applicant is requesting approval for requests approval of the proposed drug product, Sodium Nitroprusside (b) (4) Injection, 0.5 mg/mL, 50 mg/100 mL.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. Highlights are not in a minimum 8-point font.
2. There must be no white space between the Highlights (HL) and HL limitation statement.
3. In the Highlights Limitation Statement, the name of drug Product should be in upper case.
4. Each statement in HL does not have an appropriate cross reference.
5. All the text in Boxed Warning (BW) in HL is not bolded.
6. Not all the contraindications are listed in HL
7. Manufacturer phone number in HL should be toll free.
8. The Contents of Prescribing Information does not match the section and subsection headings in the Full Prescribing Information (FPI).
9. All the text in BW in FPI should be bolded.
10. Subsection headings in the FPI should be in title case.
11. The statements recommended in the Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format are

RPM PLR Format Review of the Prescribing Information

not included.

12. Your proposed label contains statements which directly contradict each other. Please review your proposed label and ensure it is accurate and consistent.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 7/15/2017. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Highlight is not in a minimum 8-point font.*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *There must be no white space between the HL and HL limitation statement.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment: *The name of drug Product is not in Upper Case.*

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- NO** 12. All text in the BW must be **bolded**.

Comment: *All the text in BW is not bolded.*

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- NO** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment: *Not all the contraindications are listed in Highlights.*

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- NO** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment: Manufacturer phone number is not toll free.

Patient Counseling Information Statement in Highlights

- N/A** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- NO** 35. All text in the BW should be **bolded**.

Comment: *All the text in BW is not bolded.*

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Verbatim statement not included.*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MARYAM K CHANGI
01/24/2017



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Division of Pediatric and Maternal Health Review

Date: 1/6/2017 **Date consulted:** 10/03/2016

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Sodium Nitroprusside (b) (4) Injection

NDA: 209387

Applicant: Exela Pharma Sciences, LLC.

Subject: Pregnancy and Lactation Labeling

Indication: immediate reduction in blood pressure, treatment of acute (b) (4) heart failure

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 209387
- (b) (4)

Consult Question: "The sponsor is updating the label to be PLLR compliant"

INTRODUCTION

On October 3, 2016, the Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy and lactation sections of sodium nitroprusside labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On May 6, 2016, Exela Pharma Sciences, LLC, submitted a 505(b) (2) new drug application for Sodium Nitroprusside (b) (4) Injection, NDA 209387. The applicant's submission relies on information from Nitropress Injection, NDA 018450, which was discontinued by Abbvie, Inc. for reasons unrelated to safety or efficacy of the drug product. Nitropress was originally approved in August, 1988, for the immediate reduction of blood pressure in adult and pediatric patients in hypertensive crisis.

The active ingredient of the applicant's sodium nitroprusside (b) (4) injection is the same of the reference listed drug (RLD) NITROPRESS (sodium nitroprusside injection). The inactive ingredients include 9mg/mL Sodium Chloride, USP (b) (4) and Water for Injection, USP (b) (4). The applicant's product is a (b) (4) injection, 0.5 mg/mL, 50mg/100mL: in an unbuffered, preservative free, non-pH-adjusted solution for intravenous administration without further dilution. (b) (4)

BACKGROUND

Drug Characteristics¹

Sodium nitroprusside is a hypotensive agent whose molecular weight is 297.95 Daltons. It is a rapid acting vasodilator, active on both arteries and veins. Its mechanism of action is relaxation of the vascular smooth muscle and consequent dilation of the peripheral arteries and veins, causing subsequent decreased blood pressure. The onset of action is within 1-2 minutes, with a half-life of approximately 2 minutes. It is rapidly distributed and is cleared by intraerythrocytic reaction with hemoglobin. The products of the nitroprusside/hemoglobin reaction are cyanmethemoglobin and the cyanide ion. Cyanide reacts with thiosulfate to produce thiocyanate, which is eliminated in the urine.

Serious adverse reactions include excessive hypotension and cyanide toxicity that can result in death.

Acute Hypertension and (b) (4) Heart Failure and Pregnancy

Acute, severe hypertension (systolic \geq 160 mm HG; diastolic \geq 110 mm HG) can occur in pregnant women or during the postpartum period. This can occur in the second half of gestation in women not known to have chronic hypertension (i.e., with preeclampsia, gestational hypertension of HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome) but also can occur in women with chronic hypertension who develop

¹ Sodium Nitroprusside proposed package insert.

superimposed preeclampsia. Acute-onset, severe hypertension that lasts 15 minutes or more is considered a hypertensive emergency. It is associated with a risk of hemorrhagic stroke or death.² Current guidelines for the treatment of severe intrapartum or postpartum hypertension include first line treatment with intravenous labetalol or hydralazine or oral nifedipine. Sodium nitroprusside “should be reserved for extreme emergencies and used for the shortest amount of time possible because of concerns about cyanide and thiocyanate toxicity in the mother and fetus or newborn.”²

Current State of the Labeling³

The most recent labeling for sodium nitroprusside lists the drug as Pregnancy Category C; labeling is not in PLR format. There are no human data in the label related to pregnancy, lactation, or reproduction. There are no studies in laboratory animals related to pregnancy; however, there are studies in pregnant ewes, where it was noted that nitroprusside was shown to cross the placental barrier and produced fatal cyanide levels in the fetus after an infusion of 25mcg/kg/min for one hour. Pregnant ewes that received infusions of 1mcg/kg/min delivered normal lambs. There are no animal data on the drug in lactation or reproduction studies. There are no interactions noted between sodium nitroprusside and contraceptives.

The current sodium nitroprusside label carries a boxed warning related to precipitous decrease in blood pressure, and in patients not properly monitored; these decreases can lead to irreversible ischemic injuries or death. Included in the boxed warning is a statement that, “except when used briefly or at low (< 2 mcg/kg/min) infusion rates, sodium nitroprusside gives rise to important quantities of cyanide ion which can reach toxic, potentially lethal levels”.

Sodium nitroprusside is contraindicated in the treatment of compensatory hypertension, in surgery in patients with known inadequate cerebral circulation, and in congenital (Leber’s) optic atrophy or with tobacco amblyopia, or in high-output heart failure such as that seen in sepsis.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁴ also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006

² The American College of Obstetricians and Gynecologists. Committee Opinion: Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period. No 623, Feb. 2015. <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Emergent-Therapy-for-Acute-Onset-Severe-Hypertension-During-Pregnancy-and-the-Postpartum-Period#1a> Accessed 10/31/2016

³ Nitropress (Sodium Nitroprusside Injection) Labeling. Drugs@FDA accessed 12/9/2016.

⁴ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

Physicians Labeling Rule⁵ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

(b) (4)

In three (b) (4) studies in pregnant ewes, nitroprusside crosses (b) (4) the placental barrier. Fetal cyanide levels were shown to be dose-related to maternal levels of nitroprusside. The metabolic transformation of sodium nitroprusside given to pregnant ewes led to fatal levels of cyanide in the fetuses. The infusion of 25 mcg/kg/min of sodium nitroprusside for one hour in pregnant ewes resulted in the death of all fetuses. Pregnant ewes infused with 1mcg/kg/min of sodium nitroprusside for one hour delivered normal lambs. For further details, the reader is referred to the Nonclinical review by Rama Dwivedi, PhD.

Applicant's Review of Literature

The applicant supplied a review of the literature using the terms, “sodium nitroprusside and pregnancy”, “sodium nitroprusside pharmacovigilance” and “sodium nitroprusside adverse effects in pregnant women.” Databases queried in this search included Google, Google Scholar, Science Direct, PubMed, DART (Toxnet), Pregnancy Exposure Registry, UpToDate, and MedWatch.

The applicant's review included several case studies^{6,7,8,9,10} and two systematic reviews^{11,12} that reported on overlapping cases. One systematic review (that included all the individual case reports that were found in the applicant's search) reported on 22 pregnant women who were treated with sodium nitroprusside and delivered 24 babies. Five of the babies were stillborn. Of the infants who were stillborn, the following was observed:

- Three mothers had severe pregnancy-induced hypertension (PIH). The gestational age at administration, the dosage and duration of sodium nitroprusside use were not described.
- One mother had severe PIH and pulmonary edema. She had been treated with magnesium sulfate and hydralazine prior to receiving sodium nitroprusside. The mother was given 3.5mg/kg of sodium nitroprusside for 15 hours. The infant was stillborn at 24 weeks and weighed 478 grams.

⁵ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

⁶ Willoughby JS. Sodium nitroprusside, pregnancy, and multiple intracranial aneurysms. *Anaesthesia and Intensive Care*. 1984. 12:358-360.

⁷ Mor-Yosef S, et al. Sodium nitroprusside during pregnancy and the fetus. *J Obstet and Gynecol*. 1990. 10(4):320-321.

⁸ Stempel JE. Use of sodium nitroprusside in complication of gestational hypertension. *Obstet and Gynecol*. 1982;60:533-538.

⁹ Rig D, et al. Use of sodium nitroprusside for deliberate hypotension during pregnancy. *Br J Anaesth*. 1981. 53:985-987.

¹⁰ Donshin Y, et al. Sodium nitroprusside for aneurysm surgery in pregnancy: Report of a case. *Br J Anaesth*. 1978. 50:849-851.

¹¹ Briggs, GG, et al. *Drugs in Pregnancy and Lactation*, 6th Edition. Lippincott Williams and Wilkens. 2001.

¹² Sass, N. Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J*. 2007. 125(2): 108-111.

- One mother had severe PIH and pulmonary edema. She had been treated with hydralazine, nifedipine, furosemide, and morphine prior to receiving sodium nitroprusside. The mother was given 7mcg/kg/min of sodium nitroprusside for 3 hours. The infant was stillborn at 34 weeks.

The authors noted that 18 women received sodium nitroprusside for severe hypertension and four women were treated for intracranial aneurysm. All of the hypertensive patients had received at least one other antihypertensive drug before receiving sodium nitroprusside. Only six publications described the sodium nitroprusside infusion rate, and the duration of sodium nitroprusside use ranged from one to 96 hours. The authors of the review noted the following:

It is impossible to conclude that sodium nitroprusside itself was directly and entirely responsible for the fetal deaths presented.... Data from the publications with the largest numbers of severely hypertensive patients suggest that maternal and fetal toxicity may not be a serious concern when sodium nitroprusside is used for short periods in emergency situations. On the other hand, the cases of fetal deaths attributed to sodium nitroprusside are poorly documented... many authors failed to report ... dosage and duration of sodium nitroprusside use, as well as the cyanide concentration in maternal blood or fetal tissue. Second, in all the cases reported... sodium nitroprusside was never the only drug involved. It was always prescribed for severely hypertensive patients after one or more antihypertensive drugs had failed to reduce blood pressure, thus making it difficult to reach the conclusion that sodium nitroprusside was directly responsible for fetal demise. The risk of perinatal death during hypertensive emergencies is considerable.¹²

The applicant's review also included animal studies relating to 1) the use of nitroprusside in pregnant ewes showing that co-infusion of sodium thiosulfate could prevent cyanide toxicity in both ewes and fetuses¹³, as well as 2) a study in guinea pigs where intracervical application of 5mg sodium nitroprusside increased cervical softening compared to vehicle at midgestation. The authors concluded that sodium nitroprusside could potentially lead to preterm delivery¹⁴.

The applicant concluded that clinical experience in pregnant women is limited and that sodium nitroprusside should only be used when the benefit to the mother is considered greater than the potential risk to the fetus.

Reviewer's Comment

The applicant's conclusions appear reasonable. See section below entitled "DPMH's Review of the Literature" for further discussion of this topic.

DPMH's Review of the Literature

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex¹⁵ using the search terms, "sodium nitroprusside and pregnancy", "sodium

¹³ Curry SC, et al. Prevention of fetal and maternal cyanide toxicity from nitroprusside with coinfusion of sodium thiosulfate in gravid ewes. *Anesth Analg.* 1997;84:1121-1126.

¹⁴ Fitkow CT, et al. Changes in light-induced fluorescence of cervical collagen in guinea pigs during gestation and after sodium nitroprusside treatment. *J Perinat Med.* 2001;29:535-543.

¹⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 11/02/16

nitroprusside and pregnant women”, “sodium nitroprusside and pregnancy and birth defects”, “sodium nitroprusside and fetal malformations”, “sodium nitroprusside and stillbirth”, and “sodium nitroprusside and miscarriage.”

Micromedex¹⁵ notes that nitroprusside sodium crosses the placenta, and states, “although nitroprusside has been used safely in pregnancy, it has several disadvantages, including potential maternal and fetal toxicity, along with cumbersome administration and monitoring requirements, and should be reserved as an alternative treatment of last resort.”¹⁶

In addition to the references reported by the applicant, the DPMH search found additional articles on hypertension and pregnancy. One article stated, “nitroprusside is rarely used, and only in an intensive care unit or operating theatre setting; its antenatal use is not desirable given that its metabolism produces thiocyanate, which can produce maternal and/or fetal toxic effects after 24 hours use (or sooner in the presence of renal dysfunction.”¹⁷ Another stated, “sodium nitroprusside is used in rare cases of hypertension not responding to other drugs, clinical findings of hypertensive encephalopathy, or both. Fetal cyanide poisoning may occur if used > 4 hours.”¹⁸ A review of 25 national/international guidelines developed for the management of arterial hypertension in adults reported that sodium nitroprusside remains the drug of choice for hypertensive crises in pregnancy, although the potential risk of fetal cyanide poisoning with prolonged administration was emphasized.¹⁹ Another reference states that sodium nitroprusside should be limited to severe intractable hypertension, acute pulmonary edema, aortic dissection and left ventricular dysfunction, with the infusion rate not exceeding 5 mcg/kg/min to reduce the risk of maternal and fetal cyanide toxicity.²⁰

Two additional case reports were located. One of these reports described the need for using a combination of nitroprusside and dobutamine to treat severe congestive heart failure in a pregnant patient.²¹ Similarly, the other case described sodium nitroprusside use to control severe maternal hypertension secondary to mitral valve disease. This last case reported that the pregnancy resulted in a stillborn infant. The infant’s liver was found to have levels of cyanide below toxic ranges, so the stillbirth may have been a result of the maternal disease rather than the medication.²²

¹⁶ Kyle PM, et al. Comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy. *Drug Safety* 1992;7:223-234.

¹⁷ Magee, LA. Treating hypertension in women of child-bearing age and during pregnancy. *Drug Safety*. 2001;24(6):457-474.

¹⁸ National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet and Gynecol*. 2000;183:(1)S1-S22.

¹⁹ Khaja A, et al. Drug treatment of hypertension in pregnancy: a critical review of adult guideline recommendations. *J Hypertension*. 2014;32(3):454-463.

²⁰ Too GT and Hill JB. Hypertensive crisis during pregnancy and postpartum period. *Sem Perinatology*. 2013. 37(4):280-287.

²¹ Nelson DM, et al. Peripartum heart failure due to primary pulmonary hypertension. *Obstet Gynecol*. 1983. 62(3 suppl):58s-63-s

²² Shoemaker CT and Meyers M. Sodium nitroprusside for the control of severe hypertensive disease of pregnancy: a case report and discussion of potential toxicity. *Am J Obstet Gynecol*. 1984. 149(2):171-3.

Summary

The published literature regarding the use of sodium nitroprusside during pregnancy is limited. Sodium nitroprusside generally is not used as a first-line treatment for severe, life-threatening hypertension, due to concerns about cyanide toxicity in the fetus.

LACTATION

Nonclinical Experience

No nonclinical data are available regarding the use of sodium nitroprusside during lactation.

Applicant's Review of Literature

The applicant did not provide information pertaining to sodium nitroprusside and lactation.

DPMH Review of the Literature

DPMH conducted a search of *Medications in Mother's Milk*, the Drugs and Lactation Database (LactMed)²³, Micromedex¹⁵, and of the published literature in PubMed and Embase using the search terms "sodium nitroprusside and lactation" and "sodium nitroprusside and breastfeeding."

In *Medications and Mother's Milk*²⁴, Thomas Hale, a breastfeeding expert, states that Nitroprusside is rated, "L4 – No Data- Possibly Hazardous."

No data are available on the transfer of nitroprusside or thiocyanate into human milk.

The half-life of the thiocyanate metabolite is approximately 3 days. Because the thiocyanate is bioavailable, some caution is advised if the mother has received nitroprusside for more than 24 hours.²⁴

Nitroprusside is referenced in LactMed²³. The following is a summary of the information regarding lactation found in that database:

Breast milk levels of nitroprusside sodium have not been measured after exogenous administration. Because of its short half-life of 2 minutes, it is unlikely to appear in breastmilk. However, its toxic metabolite, thiocyanate, is excreted into milk and can be directly toxic to the infant as well as inhibiting iodide transport into breastmilk. Cyanide is another toxic metabolite of nitroprusside that may enter breastmilk. An alternative drug is therefore preferred during breastfeeding. If use of nitroprusside sodium is unavoidable, the mother should refrain from breastfeeding.

Nitroprusside is converted with a half-life of about 2 minutes to cyanide and then to thiocyanate in the body. Both of these metabolites have longer half-lives: 7.3 hours for cyanide and an estimated 3 days to 2 weeks for thiocyanate.^{25,26}

²³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁴ Hale, Thomas (2014). *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing, pg 813.

Drug Levels:

Maternal Levels: An older study found that thiocyanate passed into human breastmilk in concentrations from 27% to 50% of maternal serum levels.²⁷ A later study found milk levels to range from 16% to 42% of maternal plasma levels.²⁸ A 2004 study found values ranging from 42% to 82%,²⁵ while a more recent study reported fractional excretion of thiocyanate that ranged between 1.4-14.4%.²⁹

Infant Levels: Relevant published information was not found.

Effects in Breastfed Infants:

Several studies have found that breastmilk iodine levels are inversely related to the mothers' thiocyanate levels, probably through inhibition of the Na/I symporter by thiocyanate.^{30,31,32,33} The authors felt that the effect of thiocyanate on iodide transport might be less pronounced than previously reported.²⁹ These low breastmilk iodine levels might pose a risk of hypothyroidism to breastfed infants whose mothers have low iodine intake.^{29,30,31,32,33}

Micromedex³⁴ notes the following; “Infant risk cannot be ruled out.”

A search of PubMed and Embase produced a few general articles on the use of antihypertensive agents in pregnancy, generally not recommending sodium nitroprusside be used during breast-feeding^{35,36} due to concerns about thiocyanate and cyanide toxicity.

²⁵ Dorea JG, et al. Maternal thiocyanate and thyroid status during breast-feeding. *J Am Coll Nutr.* 2004. 2004;23:97-101.

²⁶ Kirsten R, et al. Clinical pharmacokinetics of vasodilators. Part II. *Clin Pharmacokinet.* 1998;35:9-36.

²⁷ Funderburk CF, et al. Effect of lactation and perchlorate on thiocyanate metabolism. *Am J Physiol.* 1967;213:1371-7.

²⁸ Meberg A, et al. Smoking during pregnancy—effects on the fetus and on thiocyanate levels in mother and baby. *Acta Paediatr Scand.* 1979;68:547-52.

²⁹ Dasgupta PK, et al. Intake of iodine and perchlorate and excretion in human milk. *Environ Sci Technol.* 2008;42:8115-21.

³⁰ Vanderpas J, et al. Thiocyanate overload decreases iodine supply in iodine-deficient breast-fed infants. *Horm Res.* 2007;68(Suppl 3):53-4.

³¹ Leung AM, et al. Environmental perchlorate and thiocyanate exposures and infant serum thyroid function. *Thyroid.* 2012;22:938-43.

³² Laurberg P, et al. Iodine nutrition in breast-fed infants is impaired by maternal smoking. *J Clin Endocrinol Metab.* 2004;89:181-7.

³³ Kirk AB, et al. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. *Environ Health Perspect.* 2007;115:182-6.

³⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 10/21/16

³⁵ Kirsten R, et al. Clinical pharmacokinetics of vasodilators: Part II. *Clin Pharmacokinet.* 1998. 35(1):9-36.

³⁶ Magee LA, Adulla S. The safety of antihypertensives for treatment of pregnancy hypertension. *Exp Opin Drug Safety.* 2004. 3(1):25-38.

Summary

While data are limited, it appears that sodium nitroprusside and its toxic metabolites, cyanide and thiocyanate, pass into breast milk, and pose a potential risk for cyanide toxicity in the infant. In addition, thiocyanate has an estimated half-life of 3 days to two weeks and may affect breastmilk iodine levels. Therefore, DPMH agrees with current language in labeling that recommends that women not breast feed when treated with sodium nitroprusside.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There is no information regarding the use of sodium nitroprusside in animals and effects on fertility.

Applicant's Review of Literature

The applicant did not provide information on the effects of sodium nitroprusside on male or female reproductive potential.

DPMH review of literature

DPMH conducted a review of Micromedex, Embase and PubMed using the terms, "sodium nitroprusside and fertility", "sodium nitroprusside and contraception," sodium nitroprusside and oral contraceptives" and "sodium nitroprusside and infertility." The search revealed the following studies related to sodium nitroprusside and in *in vitro* human sperm studies and fertility in male rodents:

- 1) An *in vitro* study of human sperm showed that sodium nitroprusside significantly inhibited sperm cell motility and caused apoptosis in a dose-dependent manner. This effect was reversed by adenosine triphosphate. Sodium nitroprusside also reduced the number of sperm bound to the zona of oocytes. The study also revealed that in mice, sodium nitroprusside adversely affected embryonic development.³⁷
- 2) An *in vitro* study of mouse spermatozoa and oocyte fertilization found that sodium nitroprusside inhibited sperm motility and motion kinematics in a dose-dependent manner and decreased rates of fertilization and blastocyst formation during embryo development³⁸
- 3) A study in male rats using intrapenile injections of three different doses of sodium nitroprusside (60, 30, or 20 mcg/kg) impaired sexual arousability, vigor, and libido at the lower doses. (The highest dose was toxic and killed the treated rats.) Fertility remained unchanged.³⁹

No studies in humans on fertility or drug interactions with hormonal contraceptives were found in the literature search.

³⁷ Wu T-P, et al. Effects of nitric oxide on human spermatozoa activity, fertilization and mouse embryonic development. Archives of Andrology. 2004. 50(3): 173-179.

³⁸ Rahman MS, et al. Sodium nitroprusside suppresses male fertility in vitro. Andrology. 2014. 2(6):899-909.

³⁹ Ratnasooriya WD, et al. Sodium nitroprusside impairs sexual competence of male rats. Human and Experimental Toxicology. 2004 23(4):187-192.

Summary

DPMH discussed the above-published studies with the Nonclinical Reviewer, Rama Dwivedi, PhD, who noted that there is only one *in vivo* study showing that administration of sodium nitroprusside impairs sexual competence, and it does not affect fertility in male rats. That study has not been replicated, and it is not clear if there are other factors affecting sexual competence, such as testosterone levels or sedation. The available data do not support a significant effect of sodium nitroprusside on either fertility or hormonal contraceptive use. Therefore, Section 8.3, Females and Males of Reproductive Potential will not be included in the label.

CONCLUSIONS

Based on the literature review, DPMH has the following recommendations for Sodium Nitroprusside Injection labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Sodium Nitroprusside Injection labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” sections.⁴⁰
- **Lactation, Section 8.2**
 - The “Lactation” section of Sodium Nitroprusside Injection labeling was formatted in the PLLR format to include: the “Risk Summary,” section.⁴¹
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of Sodium Nitroprusside Injection labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of Sodium Nitroprusside Injection labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling.)

⁴⁰ Guidance for Industry: Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, A-8.1 Pregnancy, 2-Risk Summary.

⁴¹ Guidance for Industry: Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B-8.2 Lactation, 1-Risk Summary.

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/s/

CATHERINE A ROCA
01/06/2017

MIRIAM C DINATALE
01/06/2017

LYNNE P YAO
01/12/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 18, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 209387
Product Name and Strength:	Sodium nitroprusside injection, 50 mg/100 mL (0.5 mg/mL)
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences
Submission Date:	May 6, 2016 and August 29, 2016
OSE RCM #:	2016-1372
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed Sodium nitroprusside container label and carton labeling submitted on May 6, 2016 and prescribing information (PI) submitted on August 29, 2016 for risk of medication error.

This 505(b)(2) application seeks approval for a (b)(4) Sodium nitroprusside product in 50 mg/100 mL (0.5 mL/mL), and is ready to use (no further dilution required). The listed drug is Nitropress (ANDA 071961), available as 50 mg/2 mL (25 mg/mL), and requires further dilution in 250 mL to 1000 mL of sterile 5% dextrose injection depending on desired concentration.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Sodium nitroprusside container label, carton labeling, and PI to identify deficiencies that may lead to medication errors and other areas for improvement.

Prescribing Information (PI)



Container Labels and Carton Labeling

The majority of the text on the proposed container label is the same font, color, and font size, therefore decreasing the prominence of the established name and product strength. The company logo is also very prominent on the label. We also identified the use of error-prone units and abbreviations, in addition to a spelling error. The NDC number is denoted by a placeholder. The container label is also missing a usual dose statement. The lot number is not clearly differentiated from the expiration date on the container label and is missing from the carton label completely. Some parts of the label are cluttered or lack clarity. We provide recommendations in Section 4.2 to improve the clarity of the label and add important information.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed Sodium nitroprusside container label, carton labeling and PI that can be improved to increase clarity and add important information to promote the safe use of this product. We provide recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. See Appendix H for our recommendation for the proposed Sodium Nitroprusside Prescribing Information in track changes.

B. Container Label and Carton Labeling

1. Defer to CMC on the use of the appropriate established name. As currently proposed, the established name is “Sodium Nitroprusside (b) (4) Injection.”
2. Defer to CMC on the use of the appropriate package type term. As currently proposed, the labels and labeling read (b) (4) We suggest the statement “Single-dose vial – discard unused portion” (See Section 4.2 Recommendation B2).

4.2 RECOMMENDATIONS FOR EXELA

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Label and Carton Labeling)

1. Revise the established name to increase its prominence. The drug product's name is its unique identifier, thus should be presented in adequate prominence.
2. As presented, the Exela company logo is the most prominent information on the label. Revise to ensure that the graphic design does not compete in prominence with the established name per 21 CFR 201.10 (a) and 21 CFR 202.1(a)(1).
3. Ensure actual NDC number is present on the label. As presented, it is denoted by a placeholder.
4. Revise the strength per mL to "0.5 mg/mL" for consistency with the proposed Sodium Nitroprusside PI. Also, revising the strength per mL to "0.5 mg/mL" can avoid confusion where an end user could think (b) (4) is more concentrated than existing Sodium Nitroprusside drug products (25 mg/mL) when inadvertently overlooking the unit of measurement.
5. Present the route of administration without the use of an abbreviation. Revise "I.V." to "Intravenous."^a
6. Remove the negative statement (b) (4). This statement is unnecessary as the statement "Ready to Use" is already presented.

B. Container Label

1. Correct the spelling of "ifusion" to "infusion."
2. Add the statement "Single-dose vial – discard unused portion".
3. Add the usual dose statement such as "Usual dose: See prescribing information" to the side panel per 21 CFR 201.55.
4. Ensure the lot number and expiration date are labeled and differentiated.^b
5. Add the storage statement to the container label.^a
6. Add statement "Protect from light. Store in carton until ready to use." Since this proposed drug product should be protected from light according to the proposed PI, the statement "Project from light" is required on the container label per USP.^c

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^c USP General Chapter <659> Packaging and Storage Requirements

7. Revise the container label to improve readability by using layout with adequate white space, different font sizes, font color, and typography so adequate prominence is given to important information. Example container label below demonstrates our recommendation (and is for demonstration purpose only):



C. Carton Labeling

1. Add the lot number and expiration date to the carton labeling. This is required on the immediate container **AND** carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).
2. Add degree symbols to the storage temperatures so that the statement reads: Store at 20°C to 25°C (68°F to 77°F).
3. The top panel appears cluttered. Remove the statement [REDACTED] (b) (4) [REDACTED] as this already appears on the principal display panel. Also remove the company logo from this panel as it is currently the most prominent information.
4. Revise the boxing around the strength on the top panel so that the box does not overlap with the text.

To facilitate our review, please submit representative samples of revised container label and carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sodium nitroprusside that Exela submitted on May 6, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Sodium nitroprusside and the Listed Drug		
Product Name	Sodium nitroprusside	Nitropress
Initial Approval Date	N/A	August 1, 1988
Active Ingredient	Sodium nitroprusside	Sodium nitroprusside
Indications	<p>In adult and pediatric patients:</p> <ul style="list-style-type: none"> • Immediate reduction of blood pressure • Producing controlled hypotension to reduce bleeding during surgery • Treatment of acute (b) (4) heart failure 	<p>In adult and pediatric patients:</p> <ul style="list-style-type: none"> • Immediate reduction of blood pressure in hypertensive crises • Producing controlled hypotension in order to reduce bleeding during surgery • Treatment of acute congestive heart failure.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	50 mg/100 mL (0.5 mg/mL)	50 mg/2 mL (25 mg/mL)
Dose and Frequency	Start at a low rate (0.3 mcg/kg/min) with upward titration every few minutes until the desired effect is achieved or the maximum infusion rate (10 mcg/kg/min) has been reached	Recommended initial and maximal doses (0.3 mcg/kg/min and 10 mcg/kg/min, respectively). Titrate to desired effect.
How Supplied	100 mL vial	2 mL vial
Storage	Store at 20 to 25°C (68 to 77°F)	Store at 20 to 25°C (68 to 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 6, 2016, we searched the L:drive and AIMS using the terms, “nitroprusside” and “Nitropress” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 6, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Quarterly Action Agenda, Canada Safety Bulletin, Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: nitroprusside Match Exact Word or Phrase: Nitropress

D.2 Results

We did not identify any newsletters with articles relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Sodium nitroprusside labels and labeling submitted by Exela.

- Container label submitted on May 6, 2016
- Carton labeling submitted on May 6, 2016
- Prescribing information submitted on August 29, 2016

G.2 Label and Labeling Images

A. Container label

(b) (4)



^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Carton labeling

(b) (4)



APPENDIX H. PRESCRIBING INFORMATION

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

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

/s/

ASHLEIGH V LOWERY
10/18/2016

CHI-MING TU
10/18/2016



NDA 209387

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Elexa Pharma Sciences, LLC.
Attention: Johnathan E. Sterling
Vice President, Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated May 6, 2016, received May 9, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Sodium Nitroprusside (b)(4) 0.5/mL (50 mg/100 mL) Injection.

We also refer to your amendments dated June 13 and 16, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 9, 2017. We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 9, 2017.

During our filing review of your application, we identified the following potential review issues:

Regulatory:

A 505(b)(2) application contains “full reports of investigations” of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Therefore, in general, reliance on an approved ANDA is not acceptable to support a proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide an appropriate patent certification or statement with respect to each patent listed in FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)). Please also note that reliance on FDA’s finding of safety and/or effectiveness for a discontinued listed drug is contingent on FDA’s finding that the drug was not discontinued for reasons of safety or effectiveness

Biopharmaceutics:

We acknowledge your request to waive the requirement for the submission of in vivo bioavailability (BA) and/or bioequivalence (BE) data under 21 CFR 320.22(b). However, be aware that your proposed drug product does not appear to satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1). Under this regulation, a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

However, your proposed drug product does not contain the same concentration of nitroprusside as the listed drug and does not contain the same inactive ingredient as the listed drug. Therefore, a justification for these differences should be provided. We have concerns regarding the potential impact of these changes on the disposition kinetics of nitroprusside after administration of your proposed drug product in relation to the listed drug product. To address our concerns and in support of your biowaiver request to be considered under 21 CFR 320.24(b)(6), submit the following information in the NDA:

- Formulation (qualitative and quantitative composition) before and after dilution, dosage form, administered volume, etc., for the proposed drug product and the listed drug in a side-by-side comparison table.
- Comparative physicochemical data for the proposed drug product and the diluted listed drug product. The measurements should be done in triplicate for each lot tested. Include a justification for any differences in the formulation’s composition, pH, osmolality, dosage, mode of administration, drug concentration, administered volume, etc., relative to the diluted listed drug product.

- As supporting evidence, provide data and/or published literature results regarding the effects of the additional excipients in your proposed drug product on the disposition kinetics of nitroprusside in human subjects.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. The labeling contained in your submission dated June 13, 2016 is not in compliance with PLLR. Therefore, resubmit labeling in PLLR format.

The submission should include:

- a review and summary of the available published literature regarding nitroprusside use in pregnant and lactating women
- an interim or final report of an ongoing or closed pregnancy registry (if applicable)
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.
- Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidance.

In addition, the PI for a drug submitted under a 505(b)(2) application does not need to be identical to the PI for the reference drug. The PI for a 505(b)(2) application must meet all labeling regulatory requirements, should be consistent with labeling regulations and guidance recommendations, and should reflect currently available information for safe and effective use of the 505(b)(2) drug. When resubmitting the Prescribing Information, we encourage you to update labeling so that it provides updated information on the safe and effective use of your product.

As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. Highlights are not in a minimum 8-point font.
2. There must be no white space between the Highlights (HL) and HL limitation statement.
3. In the Highlights Limitation Statement, the name of drug Product should be in upper case.
4. Each statement in HL does not have an appropriate cross reference.
5. All the text in Boxed Warning (BW) in HL is not bolded.
6. Not all the contraindications are listed in HL
7. Manufacturer phone number in HL should be toll free.
8. The Contents of Prescribing Information does not match the section and subsection headings in the Full Prescribing Information (FPI).
9. All the text in BW in FPI should be bolded.
10. Subsection headings in the FPI should be in title case.
11. The statements recommended in the Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format are not included.
12. Your proposed label contains statements which directly contradict each other. Please review your proposed label and ensure it is accurate and consistent.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by August 12, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, please call Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
07/15/2016

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 # 209387	NDA Supplement #: S- N/A	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: not submitted Established/Proper Name: Sodium Nitroprusside Dosage Form: Injection Strengths: 50 mg sodium nitroprusside (b) (4) in sterile water for injection		
Applicant: Exela Pharma Sciences, LLC Agent for Applicant (if applicable):		
Date of Application: May 9, 2016 Date of Receipt: May 9, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: March 9, 2017		Action Goal Date (if different):
Filing Date: July 8, 2016		Date of Filing Meeting: June 13, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Immediate reduction of BP of adult and pediatric patients in hypertensive crisis. For producing controlled hypotension in order to reduce bleeding during surgery. Treatment of (b) (4).		
Type of Original NDA:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

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Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher

Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): Pre-IND 127676

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>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 electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Requested a new sheet on 6/7/16 via email as the original did not include the NDA #.
<u>User Fee Status</u> <i>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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> NA			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input checked="" type="checkbox"/>	<input type="checkbox"/>																		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• 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)].	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• 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)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes , please list below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	

If yes, # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input checked="" type="checkbox"/> Non-CTD <input type="checkbox"/> 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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>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 (3397/3792), 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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Only a typed and signed patent certification letter. Comment in 74 day letter
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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	No clinical studies
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>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].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act 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..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

PREA				
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Same active ingredient, dosage form, route of administration, dosing regimen. Review team concurred
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BCPA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labeling <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		SPL requested, sponsor replied they commit to supplying prior to action
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		Not originally
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Emailed on 5/12 requesting PLR and 6/8 requesting an update. Sponsor submitted prior to filing with many obvious errors
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input type="checkbox"/> <input type="checkbox"/>	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Emailed on 5/12 requesting PLLR and 6/8 requesting an update. Sponsor indicated they updated label to PLR/PLLR and resubmitted. Only PLR, not PLLR was submitted though.
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>	X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Meeting cancelled after preliminary comments (10/7/15) 2 follow up advice letters regarding preliminary comments
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>		X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 13, 2015

BACKGROUND: This application for sodium nitroprusside is being submitted by Exela Pharma Sciences, LLC as a 505(b)(2) application. For labeling they are referencing the RLD being relied upon from Hospira ANDA 071961

There is a pre-IND associated with this application in which the sponsor requested a meeting to discuss the planned NDA. The meeting was cancelled after the preliminary responses were sent. Subsequently, the sponsor sent 2 additional communications requesting advice in order to prepare for the submission. Exela states that the difference between the two products is the inactive ingredients. The new formulation contains 9 mg/mL Sodium Chloride, is unbuffered, preservative free, non pH-adjusting and is ready for direct injection without further diluting unlike the RLD. There is no new clinical data in support of this NDA, only CMC and biopharmaceutics. The sponsor did not submit in PLR nor PLLR originally. They submitted PLR prior to filing but not PLLR. In addition to CMC and Biopharmaceutics, Clinical, Clinpharm and Nonclinical will review the label. Application will be filed with 74 day comments.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alexis Childers	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Mohan Sapru		Y
Division Director/Deputy	Norman Stockbridge		Y
Office Director/Deputy	Stephen Grant		Y
Clinical	Reviewer:	Fred Senatore	Y
	TL:	Martin Rose	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Ju-Ping Lai	Y
	TL:		N
• Genomics	Reviewer:	NA	
• Pharmacometrics	Reviewer:	NA	
Biostatistics	Reviewer:	NA	
	TL:	NA	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ramadevi Dwivedi	Y
	TL:	Albert DeFelice	N
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC) Review Team:	ATL:	Mohan Sapru	Y
	RBPM:	Maryam Kord Bacheh Changi	Y
• Drug Substance	Reviewer:	Rao Kambhampati	N
• Drug Product	Reviewer:	Rao Kambhampati	N
• Process	Reviewer:	NA	
• Microbiology	Reviewer:	NA	
• Facility	Reviewer:	NA	
• Biopharmaceutics	Reviewer:	Om Anand	Y
• Immunogenicity	Reviewer:	NA	
• Labeling (BLAs only)	Reviewer:	NA	
• Other (e.g., Branch Chiefs, EA Reviewer)	NA		
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	NA	
	TL:	NA	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Zarna Patel	N
	TL:	NA	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Ashely Lowery	Y
	TL:	NA	
OSE/DRISK (REMS)	Reviewer:	NA	

	TL:	NA	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers/disciplines			
<ul style="list-style-type: none"> • Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	NA	
	TL:	BA	
Other attendees	NA		
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>Reliance of FDA's findings up safety and efficacy. They mentioned the RLD which is an ANDA and will be asked to reference the NDA.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

If no, explain:	
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
CLINICAL	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Relying on previous findings of safety and efficacy.
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable

<p>Comments:</p>	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): TBD in October

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	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.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)

<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

ALEXIS T CHILDERS
06/29/2016