

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209387Orig1s000

SUMMARY REVIEW



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.

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
03/07/2017

Cross-Discipline Team Leader Review

NDA 209387(Sodium Nitroprusside in 0.9% Sodium Chloride Injection)

Date	28-February-2017
From	Mohan Sapru, M.S., Ph.D.
Subject	Cross-Discipline Team Leader Review
Type of Application	505(b)(2)
Applicant	Exela Pharma Sciences, LLC
Date of Receipt	06-May-2016
PDUFA Goal Date	09-March-2017
Proprietary Name	Not finalized
Drug Name/Dosage Form	Sodium Nitroprusside in 0.9% Sodium Chloride Injection
Route of Administration	Intravenous Infusion
Strength	50 mg/100 mL (0.5 mg/mL)
Proposed Indication(s)	<ul style="list-style-type: none"> • Immediate reduction of blood pressure • Producing controlled hypotension to reduce bleeding during surgery • Treatment of (b) (4) heart failure
Recommended:	Approval

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

A. CMC Review Team:

Sharon Kelly (Drug Substance)
Rao Kambhampati (Drug Product)
Kumar Janoria (Process)
Yuansha Chen (Microbiology)
Om Anand (Biopharmaceutics)
Christina Capacci-Daniel (Manufacturing Facilities)
Mohan Sapru (Application Technical Lead)

B. OPQ Integrated Quality Review; in PANORAMA, dated 28-February-2017

C. Executive Summary and Final OPQ Recommendation; in PANORAMA, dated 28-February-2017

D. DMEPA Review (Ashleigh Lowery); in DARRTS, dated 31-January-2017

E. OPDM Memo (Zarna Patel), in DARRTS, dated 31-January-2017

F. DPMH Review (Catherine Roca), in DARRTS, dated 01-January-2017

1. Background

The applicant, Exela Pharma Sciences, LLC, sought U.S. marketing approval for Sodium Nitroprusside in 0.9% Sodium Chloride Injection under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR §314.54. The referenced listed drug (RLD) is Hospira's Nitropress® (Sodium Nitroprusside Injection).

The parenteral route of administration of the proposed drug product is the same as that of the RLD. The RLD NITROPRESS® (Sodium Nitroprusside Injection) is not suitable for direct injection because the solution must be further diluted in sterile 5% dextrose injection before infusion. However, Exela's proposed formulation, Sodium Nitroprusside (b) (4) Injection, is intended for direct intravenous infusion without further dilution. The proposed formulation is indicated for the immediate reduction of blood pressure of adult and pediatric patients in hypertensive crisis, and for the treatment of acute (b) (4) heart failure.

No new clinical data have been provided in support of Exela's proposed drug product because the current application relies on the Agency's determination of safety and efficacy for previously approved RLD i.e., Nitropress® (Sodium Nitroprusside Injection).

2. Chemistry, Manufacturing and Controls (CMC)

Drug Substance: The drug substance Sodium Nitroprusside (as dihydrate) is freely soluble in water, and does not exhibit isoelectric point, chirality, and isomerism. For all CMC details concerning Sodium Nitroprusside, USP, including structural characterization, manufacturing processes, control strategies, and process controls that ensure consistent production of the of the drug substance, the applicant has cross-referenced the drug master files (DMFs # (b) (4)) which have been reviewed by CMC reviewer and found to be adequate to support the approval of this NDA.

Drug Product: The applicant has proposed a ready-to-use formulation (Sodium Nitroprusside in 0.9% Sodium Chloride Injection) version of the RLD i.e., previously FDA approved Nitropress® (Sodium Nitroprusside Injection). The proposed formulation is a sterile, unpreserved, single dose, solution intended for intravenous infusion without further dilution. Each mL contains 0.5 mg of Sodium Nitroprusside, USP, 9 mg of sodium chloride, USP in Water for Injection, USP. None of the compendial excipients i.e., sodium chloride, USP, and Water for Injection, USP, used in the manufacture of the drug product, are produced from any materials of human or animal origin. Hence, there is no reason to suspect the presence of Bovine Spongiform Encephalopathy infectious agent in the excipients. Regarding comparison of Exela's formulation with the Hospira's RLD, the active ingredient concentration of the RLD is 25 mg/mL (50 mg/2 mL) and is diluted with 5% dextrose for injection (DFI) prior to intravenous infusion. The active ingredient concentration in Exela's proposed drug product is 0.5 mg/mL (50 mg/100 mL). The RLD product contains only Water for Injection, USP (b) (4), whereas, Exela's proposed formulation contains Sodium chloride, USP as a (b) (4), and Water for Injection, USP (b) (4).

Biopharmaceutics Aspects: Based on review of biopharmaceutical aspects of NDA submission, there are no outstanding issues. The applicant's request for a waiver of the requirement to conduct in vivo BA/BE studies for the proposed drug product is acceptable.

Microbiological Aspects: The sterility assurance validations supporting the proposed formulation are acceptable. Specifically, the bacterial endotoxin specification has been established at (b) (4) to ensure that the finished product complies with USP requirements for bacterial endotoxins based on the maximum total daily dose. The proposed tests and acceptance criteria for container closure integrity, sterility, and bacterial endotoxins tests are acceptable. The microbiology reviewer has recommended approval for this NDA from a quality microbiology perspective.

Container Closure System: The drug product is filled into amber, USP Type I, molded glass vials, sealed with stoppers and oversealed with aluminum Flip-Off overseals. Since the drug product solution is sensitive to light, the amber vial is packaged in a secondary carton. Using the commercial container closure system, stability of the product has been demonstrated based on 12-month long-term and 6-month accelerated stability data.

Manufacturing Facilities Review/Inspection: Per facilities status communication and review in PANORAMA, dated 27-February-2017, the Office of Process and Facilities has issued an overall "acceptable" recommendation for all manufacturing facilities supporting this NDA.

Final CMC Approval Recommendation: As per OPQ's Integrated Quality Review and recommendation (in PANORAMA, dated 28-February-2017), the Application Technical Lead (ATL) has recommended approval for this NDA from CMC/quality perspective.

3. Clinical Pharmacology

N/A

4. Non-Clinical Pharmacology/Toxicology

N/A

5. Clinical/Statistical-Efficacy

N/A

6. Safety

N/A

7. Advisory Committee Meeting

N/A

8. Pediatrics

N/A

9. Other Relevant Regulatory Issues

N/A

10. Labeling

Per NDA submission, the applicant proposed to label the product as: Sodium Nitroprusside (b) (4) Injection. However, the CMC review team alerted the applicant to the fact that usage of term “Premixed Injection” is not acceptable. To comply with *USP General Chapter <1121> Nomenclature*, the applicant agreed to Agency recommendation to label the product as: Sodium Nitroprusside in 0.9% Sodium Chloride Injection or Proprietary name (Sodium Nitroprusside) in 0.9% Sodium Chloride Injection. The proposed proprietary name Nipride RTU is still under review. The product must to be delivered by a volumetric infusion pump because small variations in infusion rate can potentially lead to wide, undesirable variations in blood pressure. The recommendation is to initiate infusion of sodium nitroprusside at a rate of 0.3mcg/kg/min, and titrate every few minutes until the desired effect is achieved or the maximum recommended infusion rate of 10 mcg/kg/min has been reached. Instructions for product administration and overdosing warnings concerning excessive hypotension, and cyanide poisoning are appropriately stated in the labeling. At this stage, a final multidisciplinary labelling review is underway but there are no labeling issues that are expected to impact the approvability of this NDA.

11. Risk Benefit Assessment

This ready-to-use product eliminates the reconstitution step, thereby; reducing the time the nurse or pharmacist spends for formulation preparation prior to administration, and potentially reduces the risk of medical error. This NDA relies on the Agency’s previous finding of safety and effectiveness for the reference listed drug, Nitropress® (Sodium Nitroprusside Injection; NDA 018450) by Abbvie Inc. The NDA 018450 was withdrawn on September 17, 2003. Per Federal Register information, Nitropress® was not discontinued or withdrawn for safety or efficacy reasons. The differences in inactive ingredients between the RLD and the proposed formulation are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via the intravenous infusion. In addition, the difference in the administered volume and infusion rate are not expected to affect the safety and efficacy of the proposed drug product. Regarding the total sodium content of the proposed formulation, each vial (100 mL) of the proposed drug product solution contains a total of (b) (4) of total sodium (b) (4). Based on assessment of clinical implications, the clinical review team found the total sodium content in the formulation acceptable.

12. Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur 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.

Mohan K. Sapru -S
Digitally signed by Mohan K. Sapru -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Mohan K. Sapru -S,
0.9.2342.19200300.100.1.1=200058931
5
Date: 2017.03.01 15:37:38 -05'00'

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

/s/

MOHAN K SAPRU
03/01/2017