CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214313Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review Addendum

Date	15-January-2021
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	CDTL Review Addendum
NDA	214313
Type of Application	505(b)(2)
Applicant	Baxter Health Corporation
Date of Receipt	16-March-2020
PDUFA Goal Date	16-January-2021
Established/Proper Name	Norepinephrine Bitartrate in 5% Dextrose Injection
Dosage forms; Strength	Parenteral; 4 mg Norepinephrine in 250 mL of 5% dextrose, and 8 mg Norepinephrine in 250 mL of 5% dextrose
Route of Administration	Intravenous (IV) Infusion
Proposed Indication(s)	For restoration of blood pressure in adult patients with acute hypotensive states
Regulatory Action	**Approval as a combination product**

I. CDTL Review Update

This addendum is aimed to capture briefly an update regarding combination product designation for the proposed product i.e., Norepinephrine Bitartrate in 5% Dextrose Injection, and its recommended approval as a combination product.

II. Brief Background

The proposed product consists of drug (Norepinephrine Bitartrate in 5% Dextrose) that is filled into a Viaflo IV container (infusion bag), which is considered a device constituent part. Thus, the Agency has determined that the proposed product is a combination product within the meaning of section 503(g) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 353(g)) and Title 21 of the Code of Federal Regulations (CFR) section 3.2(e)(2).5. As a part of NDA review, the Agency, via an Information Request (dated June 16, 2020), communicated the following to Applicant: "Your product includes the drug product, Norepinephrine Bitartrate in 5% Dextrose for Injection, that is filled into an IV container, which is a device constituent part. As such, your product is a combination product as defined under 21 CFR 3.2(e). Combination products are subject to the current good manufacturing practice (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. Acknowledge that your product is a combination product and revise your Form FDA 356h

accordingly." (b) (4) The Agency held a teleconference with the Applicant on September 16, 2020 and reiterated the underlying rationale for classifying the proposed product as a combination product. Subsequent to the teleconference, (b) (4)

III. Multidisciplinary Review Assessment

a) Based on input from the Office of Combination Products, Office of Product Quality (OPQ), Office of Chief Council, OND and OPQ policy, there is convergence of recommendations to designate and approve Norepinephrine Bitartrate in 5% Dextrose Injection as a combination product.

b) As documented in the original CDTL Review (refer to CDTL Review in DARRTS, dated September 14, 2020), all the reviews of this application recommended approval, and I concur with the reviewers.

c) As shown below, an overall inspection recommendation of 'approval' for the facilities listed in the NDA was made on August 17, 2020. All the facilities continue to be adequate.

Submission Overall Manufacturing Facility Status

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	8/17/2020	Pending	NDA-214313-ORIG-1

d) Because there is a trend for a decrease in product 'assay' values coupled with increase in impurity levels, the Applicant's initially proposed (b) (4)-month expiration period is not supported by the product stability studies. Based on stability data, an expiration period of 7 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial packaging. Product excursions are permitted to 15-30°C (59-86°F).

e) The Division's labeling recommendations have been accepted by the Applicant and are reflected in the most recent version of the product labeling.

IV. Recommended Regulatory Action

The proposed product i.e., Norepinephrine Bitartrate in 5% Dextrose Injection (NDA 214313) is recommended for approval as a combination product.

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/s/

MOHAN K SAPRU
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NORMAN L STOCKBRIDGE
01/15/2021 10:00:42 AM

Cross-Discipline Team Leader Review

Date	14-September-2020
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	Cross-Discipline Team Leader Review
NDA	214313
Type of Application	505(b)(2)
Applicant	Baxter Health Corporation
Date of Receipt	16-March-2020
PDUFA Goal Date Action Goal Date	16-January-2021 16-September-2020
Established/Proper Name	Norepinephrine Bitartrate in Dextrose Injection
Dosage forms; Strength	Parenteral; 4 mg Norepinephrine in 250 mL of 5% dextrose, and 8 mg Norepinephrine in 250 mL of 5% dextrose
Route of Administration	Intravenous Infusion
Proposed Indication(s)	Indicated for restoration of blood pressure in adult patients with acute hypotensive states
Regulatory Action	**Approval**

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

Material Reviewed/Consulted	Review Team
OPQ's Integrated Quality Review (DARRTS, dated 20-August-2020)	Zhengfu Wang, Steven Hertz, Nadia Ahmed, Dustin Thomas, and Akm Khairuzzaman
Non-Clinical Review (DARRTS, dated 14-August-2020)	Rama Dwivedi, and Xuan Chi
DMEPA Review (DARRTS, dated 9-September-2020 and 18-August -2020)	Mariette Aidoo, and Hina Mehta
OPDP Labeling Consult Review (DARRTS, dated 25-August-2020)	Puja Shah, James Dvorsky

OPQ: Office of Pharmaceutical Quality; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion.

1. Background

The Applicant, Baxter Health Corporation, has sought U.S. marketing approval for Norepinephrine Bitartrate in Dextrose Injection, for intravenous infusion, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Norepinephrine is a sympathomimetic catecholamine that is indicated for blood pressure control in certain acute hypotensive states. For the approval of this NDA, the applicant relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) i.e., LEVOPHED (Norepinephrine Bitartrate Injection, 1mg/mL; reference NDA 007513, held by Hospira). Per approved labeling, Levophed for intravenous infusion requires dilution with 5% dextrose prior to use. As a ready-to-use premix, Baxter's proposed Norepinephrine Bitartrate in 5% Dextrose Injection does not require dilution prior to intravenous administration. The LD contains sodium metabisulfite, an antioxidant, as an additional inactive ingredient. Use of pre-mixed solutions is one of preventive ways to prevent medication errors and associated complications. Due to a potential drug shortage related to the current Covid-19 pandemic, this NDA for Norepinephrine Bitartrate in Dextrose Injection has been reviewed under a 6-month expedited review clock.

2. Product Quality

2.1. Drug Substance (Norepinephrine Bitartrate)

Norepinephrine bitartrate is a compendial (USP & Ph. Eur.) drug substance that exists as norepinephrine bitartrate monohydrate. All CMC information, including structural characterization, impurities, physicochemical properties, manufacturing, specification, batch analysis and stability data, is cross-referenced to DMF (b) (4), which has been reviewed and found adequate. The additional details provided in the NDA, including the release specification, which involves testing of critical quality attributes, are adequate.

2.2. Drug Product

The proposed drug product, Norepinephrine Bitartrate in 5% Dextrose Injection is a ready-to-use sterile aqueous solution administered by intravenous infusion. The product is presented in following two (2) configurations:

- 4 mg equivalent of norepinephrine in 250 mL of 5% dextrose: Each I mL contains the equivalent of 16 micrograms of norepinephrine base, supplied as 31.90 micrograms per mL of norepinephrine bitartrate monohydrate.
- 8 mg equivalent of norepinephrine in 250 mL of 5% dextrose: Each I mL contains the equivalent of 32 micrograms of norepinephrine base, supplied as 63.80 micrograms per mL of norepinephrine bitartrate monohydrate.

The recommended clinical dose and infusion rate for the proposed Norepinephrine Bitartrate in 5% Dextrose Injection is identical to the LD. All the inactive ingredients are below the levels provided in Inactive Ingredients Database (IID) maintained by the FDA. Product release specification, involving testing of product critical quality attributes such as identity, assay for L-norepinephrine, enantiomeric purity, impurities, (b) (4), pH, osmolality, particulate matter, sterility, elemental impurities (per USP <232>/ICH Q3D requirements), and bacterial endotoxins, is adequate. The analytical procedures have been adequately validated.

2.2.1. Manufacturing: The manufacturing process involves [redacted]. The validated process for [redacted] sterilization, and container closure integrity testing are adequate. The Applicant has demonstrated that the drug product can be manufactured with consistent quality and purity. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

2.2.2. Microbiological Aspects: The proposed drug product is [redacted] sterilized. The product sterility is the key critical quality attribute of the proposed product. Manufacturing of the drug product is adequately controlled for microbiological attributes at various stages of the process. Microbiology tests, i.e. sterility, and bacterial bioburden testing are performed as per USP <71> and USP <85>, respectively, as part of the release testing of the finished product.

2.2.3. Biopharmaceutics Aspects: The Applicant has not provided any *in-vivo* bioequivalence studies. Instead, the Applicant proposed to establish a bridge, per 21 CFR 320.24(b)(6), between the LD and the proposed drug product through comparisons of formulation and physiochemical data; demonstrating that the differences will not impact the *in vivo* performance of the proposed drug product. Specifically, the Applicant has demonstrated comparable pH, osmolality, specific gravity, and viscosity characteristics between the proposed drug product and the LD. Minor differences observed with respect to surface tension are not expected to impact the proposed drug product's *in vivo* performance. Additionally, the Applicant has provided supporting comparative data concerning attributes such as assay and levels of related compounds and enantiomeric impurity. The totality of data and information support the conclusion that the minor formulation differences between the LD and the proposed drug product are not expected to demonstrate meaningful differences in the *in vivo* drug performance. Thus, from a biopharmaceutics perspective, bridging has been established between the proposed drug product and the LD.

2.3. Assessment of Manufacturing Facilities: Regarding the listed manufacturing and testing facilities for this NDA, there are no outstanding cGMP issues and are deemed acceptable. Specifically, both the drug product and drug substance facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

2.4. Expiration Date & Storage Conditions: The proposed to-be-marketed drug product is packaged in Baxter's Viaflo container closure system. Study results indicate the suitability of the Viaflo container for its intended use of packaging drug product solutions. Because there is a trend for decrease in product 'assay' values coupled with increase in impurity levels, the Applicant's initially proposed [redacted]-month expiration period is not supported by the product stability studies. Based on stability data, an expiration period of 7 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial packaging. Product excursions are permitted to 15-30°C (59-86°F).

2.5. Integrated Quality Assessment Conclusion: From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214313 (Norepinephrine Bitartrate in Dextrose Injection) is recommended for approval.

3. Non-Clinical Pharmacology/Toxicology

The applicant, in compliance with the principles outlined in ICH-M7(R11) and ICH-Q3B (R22), conducted a (Q)SAR analysis (using two complementary methodologies) to assess the mutagenic potential of impurities. In addition, a 14-day repeated-dose general toxicity (GLP) study in rats has been conducted, with a clastogenic (micronucleate erythrocyte formation) endpoint incorporated into the study, to qualify product impurities. Based on evaluation of results from these studies, the identified impurities in the proposed drug product that are present at a higher level than in the LD and/or exceed the appropriate qualification threshold per ICH-Q3B(R2), are considered qualified from the Pharmacology/Toxicology perspective.

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation

N/A

6. Clinical Studies/Financial Certification Disclosure

No clinical studies have been performed in support of this 505(b)(2) NDA. Hence, there is no financial information to disclose.

7. Advisory Committee Meeting

N/A

8. Pediatrics, and Other Relevant Regulatory Issues

None of the PREA criteria apply to this application. Hence, the Applicant is exempt from this requirement.

9. Labeling

Based on multidisciplinary review, the Division's labeling recommendations have been accepted by the Applicant and are reflected in the most recent version of the product labeling.

10. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

  All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review, an expiration period of 7 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial container closure system. Product excursions are permitted to 15°C -30°C (59°F -86°F).

- **Risk Benefit Assessment**

The current NDA relies on FDA's previous finding of safety and efficacy for the LD i.e., LEVOPHED (Norepinephrine Bitartrate Injection. The proposed indication for the proposed drug product has been previously approved for the LD. The applicant's proposed to-be-marketed drug product is essentially similar to the LD, as it has the same active moiety and delivers the same amount of drug to the patient. The differences in inactive ingredients between the proposed product and the LD have been adequately justified by the Applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for currently marketed LD. The non-clinical, and clinical information concerning clinical efficacy and safety of norepinephrine available in published literature does not warrant any change in current assessment of the risk-benefit profile of norepinephrine.

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/s/

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