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APPLICATION NUMBER:

214628Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	5-October-2022
From	Mohan Sapru, M.S., Ph.D. Branch Chief, New Drug Products Division III, Branch V Office of New Drug Products/OPQ
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	CDTL Review
NDA	NDA 214628; Norepinephrine in Sodium Chloride Injection
Type of Application	505(b)(2)
Applicant	Nevakar Injectables, Inc.
Date of Receipt	04-August-2022
PDUFA Goal Date	07-October-2022
Established/Proper Name	Norepinephrine in Sodium Chloride Injection
Strength	4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL)
Route of Administration	Intravenous (IV)
Proposed Indication(s)	For restoration of blood pressure in adult patients with acute hypotensive states
Regulatory Action	**Approval**

This CDTL 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 16-September-2022)	Zhengfu Wang, Akm Khairuzzaman, Krishna Ghosh, Julia Marre, and Theodore Carver
Non-Clinical Review (DARRTS, dated 15-April-2022)	Rama Dwivedi, and Xuan Chi
DMEPA Review (DARRTS, dated 12-September- 2022)	Hina Mehta
OPDP Review (DARRTS, dated 11-July-2022)	Meena Savani

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

1. Background

In accordance with Section 505(b)(2) of the FD&C Act, the Applicant submitted the original NDA 214628 on August 17, 2020. FDA issued a Complete Response Letter on June 14, 2021, mainly because the drug product manufacturing facility had 'withhold' status due to unresolved Form 483-

listed deficiencies. For details refer to the original CDTL Review (DARRTS, dated June 09, 2021). The Applicant resubmitted the NDA on 04-August-2022. For the approval of this NDA, the Applicant relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) LEVOPHED® (Norepinephrine Bitartrate Injection, USP) approved under NDA 007513 (Hospira, Inc.). This resubmitted application is seeking approval for the same clinical indication, route of administration, dose, and dosing regimen as those of the LD.

2. Product Quality

Norepinephrine in Sodium Chloride Injection is supplied as a clear, colorless sterile solution in a 250 mL non-PVC infusion bag with single function connector system consisting of a port and cap, packaged individually in an aluminum foil pouch with an oxygen scavenger. The single dose sterile solution, supplied as a ready-to-use intravenous infusion bag for intravenous use, does not require further dilution. Each mL contains the equivalent of 16 or 32 or 64 micrograms of norepinephrine base supplied as 31.90 or 63.80 or 127.6 micrograms per mL of norepinephrine bitartrate monohydrate. In addition, each mL of solution contains 0.01 mg edetate disodium dihydrate as a metal chelator and 9.0 mg sodium chloride for isotonicity. The updated drug product specification is adequate.

2.1. Manufacturing, and Manufacturing Facilities: The Applicant has adequately addressed all manufacturing process-related comments and deficiencies in this NDA resubmission. The drug product manufacturing facility (b) (4) had previously a 'withhold' status due to unresolved Form 483-listed deficiencies, resulting in FDA issuing a Complete Response Letter on June 14, 2021. As a part of review of this resubmitted NDA, a reinspection was conducted for this facility. Based on the reinspection, all the previously facility deficiencies have been satisfactorily addressed. Therefore, all listed facilities for the resubmitted NDA 214628 are deemed acceptable.

3. Integrated Quality Evaluation

OPQ's integrated review concludes that this resubmitted NDA meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have. As such, OPQ has recommended approval of this NDA from a quality perspective.

4. Non-Clinical Pharmacology/Toxicology

Per this NDA resubmission, the Applicant identified an additional impurity (b) (4) (b) (4). Based on the weight of evidence approach per ICH-M7(R1) and ICH-S2(R1), (b) (4) impurity is considered non-genotoxic and a Class 5 impurity. This is based on (Q)SAR analysis (negative) and the results from the battery of genotoxicity testing (negative Ames assay, positive in vitro mammalian cell chromosomal aberration assay, and negative in two in vivo genotoxicity assays). Considering the endogenous nature of the impurity (b) (4), the acute use of the drug product for a life-threatening indication and the safety margin obtained from 13-weeks repeated dose toxicology studies, the proposed specification level of (b) (4)% for (b) (4) (b) (4) for the drug product is considered acceptable from the Pharmacology/Toxicology perspective. No new nonclinical safety signals were identified by the literature search conducted for this resubmission.

5. Clinical Pharmacology

N/A

6. Statistical-Evaluation

N/A

7. Clinical Studies, and Financial Certification Disclosure

No clinical studies were performed in support of this 505(b)(2) NDA. The Integrated Summary of Safety captured a summary of norepinephrine's safety profile drawn from the approved label and the literature and included no new safety information. Financial certifications (Form FDA 3454 and Form FDA 3455) are not applicable to this application because no bioavailability/bioequivalence studies were performed for the proposed product.

8. Advisory Committee Meeting

N/A

9. Pediatrics, and Other Relevant Regulatory Issues

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

10. Labeling

Per the finalized product label and labeling, the Applicant has incorporated Agency's all labeling recommendations and edits.

11. Risk Benefit Assessment

The current NDA has relied on FDA's previous finding of safety and efficacy for the Listed Drug (LD). The proposed 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 proposed indication is the same as currently approved for the LD. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the currently marketed LD.

12. Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur with the review teams. Based on the OPQ's Integrated Quality Review, an expiry dating period of 24 months is granted for Norepinephrine in Sodium Chloride Injection when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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/s/

MOHAN K SAPRU
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Cross-Discipline Team Leader (CDTL) Review

Date	08-June-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
NDA	NDA 214628; Norepinephrine Bitartrate in Sodium Chloride Injection
Type of Application	505(b)(2)
Applicant	Nevakar, Inc.
Date of Receipt	17-August-2020
PDUFA Goal Date	17-June-2021
Established/Proper Name	Norepinephrine in 0.9% Sodium Chloride Injection
Strength	16 mcg/mL, 32 mcg/mL, and 64 mcg/mL
Route of Administration	Intravenous (IV)
Proposed Indication(s)	Norepinephrine is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states
Regulatory Action	**Complete Response**

This CDTL 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 04-June-2021)	Martin Haber, Akm Khairuzzaman, Krishna Ghosh, Joan Zhao, and Karthik Krishnan
Non-Clinical Review (DARRTS, dated 06-May-2021)	Rama Dwivedi, and Xuan Chi
DMEPA Review (DARRTS, dated 24-November-2020; 14-January-2021 and 24-February-2021)	Mariette Aidoo, and Hina Mehta

OPQ: Office of Pharmaceutical Quality; DMEPA: Division of Medication Error Prevention and Analysis.

1. Background

The Applicant has sought U.S. marketing approval for NDA 214628 in accordance with Section 505(b)(2) of the FD&C Act. For the approval of this NDA, the Applicant relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) LEVOPHED® (Norepinephrine Bitartrate

Injection, USP) approved under NDA 007513 (Hospira, Inc.). This application is seeking approval for the same clinical indication, route of administration, dose, and dosing regimen as those of the LD. LEVOPHED® is approved as a 1 mg/mL sterile aqueous solution in the form of the bitartrate salt in a 5 mL vial and needs to be diluted with 5% Dextrose Injection, USP or Sodium Chloride Injection solutions that contain 5% dextrose to achieve a final concentration of 4 mcg/mL before administration via intravenous infusion. The proposed product is supplied as a ready-to-use, sterile solution in single-dose 250 mL infusion bag, available at concentrations of 16 mcg/mL, 32 mcg/mL, and 64 mcg/mL. The Applicant doesn't intend to seek a proprietary name for the proposed product.

2. Product Quality

2.1. Drug Substance (Norepinephrine)

Norepinephrine, a well-established compendial drug substance, is a chiral compound and exists as norepinephrine bitartrate monohydrate. Norepinephrine manufactured by the Applicant is an R-enantiomer, which is characterized and controlled by the specific optical rotation and chiral purity tests. All CMC information about the drug substance is cross-referenced to DMF # (b) (4) which has been reviewed and found adequate. The additional CMC details provided in the NDA, including the drug substance release specification, which involves testing of critical quality attributes, are adequate.

2.2. Drug Product (Norepinephrine in 0.9% Sodium Chloride Injection)

2.2.1. Product Design, Stability and Control Strategies: The proposed drug product is a clear, colorless, sterile solution in 250 mL 0.9% sodium chloride presented in three strengths: 4 mg base/250 mL (16 mcg base/mL), 8 mg base/250 mL (32 mcg base/mL), 16 mg base/250 mL (64 mcg base/mL). Each strength of drug product is filled into a 250-mL (b) (4) non-PVC infusion bag for a single-use intravenous administration. All proposed excipients are compendial grade and their levels do not exceed the inactive ingredients database (IID) levels for the intravenous infusion route of administration based on Maximum Daily Intake (MDI). The LD contains the antioxidant metabisulfite, which is known to cause allergic reactions in the general population. In the proposed product, oxidation of norepinephrine is instead prevented by a metal chelating agent, edetate disodium (EDTA). The revised product release specification, involving testing of product critical quality attributes such as appearance, identity, assay for L-norepinephrine, enantiomeric impurity (D-norepinephrine), related substance, (b) (4), pH, osmolality, particulate matter, sterility, and bacterial endotoxins, is adequate. The current stability data and statistical analysis demonstrate that the proposed product is stable for a period of 24 months when stored at 20 – 25ºC (68 – 77ºF) in the proposed container closure system.

2.2.2. Biopharmaceutics Aspects: The proposed product has the same active ingredient, dosage form, dose, dosing regimen, and route of administration as the LD. The amount of sodium chloride content at the point of patient contact, from Nevakar's Norepinephrine in Sodium Chloride Injection and the diluted LD product, is same. Nevertheless, the proposed product differs from the LD in product concentration, use of excipients and flow rate of the infusion. Due to these differences, a biowaiver under 21 CFR 320.22(b)(1) is not feasible. The absence of sodium metabisulfite and the presence of edetate disodium dihydrate in the proposed product are

unlikely to affect the *in vivo* disposition of norepinephrine in humans in any clinically meaningful manner. A bridge between the proposed drug product and the LD has been established, per 21 CFR 320.24 (b)(6), based on comparisons of LD and proposed formulation, including their similar physiochemical properties.

2.2.3. Microbiological Aspects: 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 for sterility, and bacterial bioburden content are performed as per USP <71> and USP <85>, respectively, as part of the release testing of the finished product. The in-use hold time of 24 hours after opening from the overwrap is also supported by the microbiological data.

2.2.4. Manufacturing: The manufacturing process involves (b) (4) (b) (4)

Based on evaluation of all unit manufacturing processes, the Applicant has not demonstrated that the commercial manufacturing process is adequately controlled. Outstanding manufacturing process deficiencies include: (b) (4) (b) (4)

2.2.5. Assessment of Manufacturing Facilities:

Based on preapproval inspection of drug product manufacturing facility (b) (4), conducted in (b) (4) and evaluation of FDA 483 observations and manufacturing facility's responses, it has been concluded that the firm is not ready to manufacture commercial batches of Norepinephrine in 0.9% Sodium Chloride Injection due to lack of adequately installed and qualified commercial manufacturing equipment, inadequate process controls (b) (4), inadequate microbiological controls and environmental monitoring practices along with a lack of adequate GMP controls. Therefore, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment for this NDA is "withhold".

3. Non-Clinical Pharmacology/Toxicology

An acceptable nonclinical toxicity profile of norepinephrine is already well established as described in the approved labeling for the LD. Based on literature search, no new clinically relevant toxicity concerns are apparent. Two impurities identified during stability and observed chromatographically in the drug product at relative retention times (RRT) of (b) (4) and RRT (b) (4) are (b) (4)

(b) (4). To support the limits for the two specified impurities i.e., NMT (b) (4)% (RRT (b) (4)) and NMT (b) (4)% (RRT (b) (4)) that exceeded the qualification threshold of 0.5%, the Applicant has conducted a 28-day continuous infusion repeat-dose toxicity study, Ames test, Chromosome Aberration test and Mouse Micronucleus test. In addition, based on Agency recommendations, the Applicant has conducted 14-Day GLP continuous infusion study in rats; testing the above mentioned impurities at levels that represent at least (b) (4) the MDD ((b) (4) mg/day) corrected for the Human Equivalent Dose (HED), as per FDA guidance (FDA 2005). Based on Mammalian Erythrocyte Micronucleus Test and the results of the Bacterial Reverse Mutation Assay, the Norepinephrine Impurity Mixture (NVK004) is not considered genotoxic or mutagenic. Clastogenic effect of NVK004 Impurity Mixture is apparent at extremely high concentrations compared to potential human exposure ((b) (4)-fold or higher). Based on totality of toxicology studies, (b) (4) impurities are not considered genotoxic or hemolytic at clinically relevant dose range. However, the limited 14-Day Repeat Dose Toxicology study data suggest some adverse findings in the aorta, the arteries in the brain and lungs as a result of the administration of these two impurities at (b) (4) or (b) (4) the maximum daily dose. The pharmacology and toxicology review recommended that the Applicant revise the specification limit for these two impurities to be compliant with the qualification threshold set forth in ICH-Q3B(R2). Per Agency recommendation, the Applicant has revised acceptance limit for each of these impurities at qualification threshold of NMT (b) (4)%, which is within ICH-Q3B(R2) limits.

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 Pediatric Research Equity Act (PREA) criteria apply to this application. Hence, the Applicant is exempt from this requirement.

9. Labeling

Because of the recommended Complete Response action, product labeling has not been reviewed in detail.

10. Recommended Regulatory Action

Per the Integrated Quality Review, the OPQ's review team has made a 'Complete Response' recommendation for NDA 214628 (Norepinephrine in 0.9% Sodium Chloride Injection) because the drug product manufacturing facility (b) (4) has 'withhold' status due to unresolved Form 483-listed deficiencies. I agree with this assessment and recommend the Complete Response regulatory action for this NDA. Satisfactory resolution of all the identified deficiencies is required before this application may be approved.

A. List of Deficiencies to be Communicated to the Applicant

Facility Inspection: During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility that were conveyed to the representative of the facility at the close of the inspection. Satisfactory resolution of these deficiencies is required before this application may be approved.

B. Additional Comments/Recommendations Pertinent for NDA Resubmission

(b) (4)

(b) (4)

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/s/

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