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APPLICATION NUMBER:

215700Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Cross-Discipline Team Leader (CDTL) Review

Date	September 14, 2022
From	Michael Monteleone, MS, RAC Associate Director for Labeling, Division of Cardiology and Nephrology
Through	Norman Stockbridge, MD, PhD Director, Division of Cardiology and Nephrology
NDA	215700
Type of Application	505(b)(2)
Applicant	InfoRLife SA
Date of Receipt	November 19, 2021
PDUFA Goal Date	September 19, 2022
Established/Proper Name	Norepinephrine Bitartrate in Sodium Chloride Injection
Dosage forms; Strength	Injection; 4mg/250mL, 8mg/250mL, 16mg/250mL
Route of Administration	Intravenous infusion
Proposed Indication(s)	Norepinephrine Bitartrate in Sodium Chloride Injection is indicated to raise blood pressure in adult patients with severe, acute hypotension.
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
Non-Clinical Review (2022-04-21)	Rama Dwivedi; Xuan Chi
Division of Medication Error Prevention Analysis (2022-05-09, 2022-09-06)	Maximilian Straka; Hina Mehta
Office of Prescription Drug Promotion (2022-05-18)	Charuni Shah; Melinda McLawhorn
Integrated Quality Review (2022-07-19)	Ben Zhang, Zhengfu Wang, Akm Khairuzzaman, Theodore Carver, Upasana Sahu, Sateesh Sathigari, Zhuojun Zhao, Kimberly Raines, Jianli Xue, Nandi Bhattacharya, Grafton Adams

1. Background

The Applicant, InfoRLife SA, has sought U.S. marketing approval for Norepinephrine Bitartrate in Sodium Chloride Injection, for intravenous infusion, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Norepinephrine is a catecholamine indicated to raise blood pressure (b) (4) in adult patients with severe, acute hypotension. 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).

2. Quality Assessment Summary

2.1. Drug Substance

Norepinephrine bitartrate is a compendial (USP & Ph. Eur.) drug substance that exists as norepinephrine bitartrate monohydrate. CMC information for the drug substance is referenced to type II DMF (b) (4), which has been reviewed and found adequate. Additional details provided in the NDA, including the release specification, which involves testing of critical quality attributes, are adequate.

2.2. Drug Product

2.2.1. Product Design, Stability and Control Strategies:

The proposed drug product is a clear, colorless, sterile solution. The Applicant developed Norepinephrine in 0.9% Sodium Chloride Injection through the 505(b)(2) regulatory pathway as a "combination drug product" referencing the Listed Drug product, Levophed 4mg/4ml. The strength is expressed as "norepinephrine base" in accordance with the USP monograph for the referenced listed product. Each mL contains the equivalent of 16, 32 or 64 micrograms base of norepinephrine supplied as (b) (4) micrograms per ml of norepinephrine bitartrate monohydrate, respectively. Each strength of of drug product is (b) (4) filled to a volume of 250 mL in the 300 mL infusion bag equipped with two tubing ports and one twist off port. The Applicant provided references to relevant DMFs for the container closure system. The inactive ingredients do not exceed the IID levels for the intravenous infusion route of administration based on Maximum Daily Intake (MDI). The product release specification, involving testing of product critica quality attributes such as appearance, identity, assay (% as labeled claim L-norepinephrine), enantiomeric purity (% as D-norephinphrine), degradation product, pH, osmolarity, particulate matter, microbial contamination, and bacterial endotoxins, is adequate.

The proposed product does not contain antioxidants or other ingredients that retard oxidation, such as dextrose. The potential risk of oxidation for the proposed formulation has been evaluated by the product quality team. This risk has been found to be adequately mitigated when used and stored according to the labeled instructions by packaging the drug product immediate container in a plastic/foil overwrap that contains an oxygen scavenger and oxygen indicator.

2.2.2. Biopharmaceutics Aspects:

The applicant has provided sufficient information to support the bridge between the proposed Norepinephrine Bitartrate in Sodium Chloride Injection and the listed drug, Levophed (norepinephrine bitartrate) injection under 21 CFR 320.24(b)(6).

2.2.3. Microbiological Aspects:

The proposed drug product is (b) (4) . Manufacturing of the drug product is adequately controlled for microbiolgical attributes.

2.3. Manufacturing:

Manufacturing process includes (b) (4)

The Applicant has demonstrated that the drug product can be manufactured with consistent quality and purity. Based on the control strategy, including in-process and (b) (4) controls, the manufacturing process is adequately controlled.

2.4. Assessmet of Manufacturing Facilities:

All facilities were adequate based upon previous inspection history.

2.5. Expiration Date & Storage Conditions

The current stability data and statistical analysis demonstrate that the proposed product is stable for a period of 24 months at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Product should be used within 7 days of removal from aluminum overwrap.

3. Non-Clinical Pharmacology/Toxicology

Leachable analytes identified in the to-be marketed container closure system were evaluated by the review team. The review team concludes that the proposed permitted daily exposures (PDEs) for leachable analytes are acceptable, and the leachable analytes at the level demonstrated are considered qualified from a pharmacoly/toxicology perspective.

4. Clinical Pharmacology

Not applicable.

5. Statistical-Evaluation

Not applicable.

6. Clinical Studies/Financial Certification Disclosure

No clinical studies were conducted in support of this application. The Summary of Clinical Safety includes an updated review of safety based on literature and FAERS. No new safety information was identified.

Financial Certification Disclosure is not applicable.

7. Advisory Committee Meeting

An advisory committee was not convened for this application.

8. Pediatrics, and Other Relevant Regulatory Issues

This application does not trigger PREA.

This application was cleared from a 505(b)(2) perspective on August 4, 2022.

9. Labeling

The prescribing information for this application is substantially similar to the LD, Levophed. Carton and container labeling have been reviewed and deemed acceptable.

10. Recommendeds/Risk Benefit Assessment

10.1. Recommended Regulatory Action

This application is recommended for approval.

10.2. 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. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHAEL V MONTELEONE
09/14/2022 01:59:30 PM

NORMAN L STOCKBRIDGE
09/14/2022 02:09:04 PM