CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215875Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	March 31, 2023
From	Theodore Carver, Ph.D. Senior Pharmaceutical Quality Assessor Division III, Branch 5, Office of New Drug Products, OPQ
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Submission Type	NDA 215875
Type of Application	505(b)(2)
Applicant	PAR Sterile Products, LLC
Date of Receipt	June 22, 2022
PDUFA Goal Date	April 22, 2023
Established/Proper Name	Epinephrine in Sodium Chloride Injection
Strength	8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, and 40 mcg/mL
Route of Administration	Intravenous (IV)
Proposed Indication(s)	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
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 15-March 2023)	Ben Zhang, Zhengfu Wang, Rao Kambhampati, Allison Aldridge, Rose Xu, and Theodore Carver
Nonclinical Review, (DARRTS, dated 12-January 2023)	Rama Dwivedi and Xuan Chi
DMEPA Review (DARRTS, dated 2-March 2023)	Jody Kundreskas and Hina Mehta

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

1. Background

The Applicant, PAR Sterile Products, LLC (PAR), has submitted NDA 215875 for marketing approval of five new pre-diluted strengths of epinephrine in 0.9% saline solution, as a treatment to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. PAR has not conducted any nonclinical or clinical studies with Epinephrine in 0.9% Sodium Chloride Injection and relies on FDA's previous findings of safety and effectiveness for the listed drug, ADRENALIN® (epinephrine injection) 1 mg/mL, approved under NDA 204200 (Par Pharmaceutical, Inc.) as 1 mg/mL single dose vials and under NDA 204640 (Par Pharmaceutical, Inc.) as 30 mg/30 mL (1 mg/mL) multiple dose vials. The Epinephrine in 0.9% Sodium Chloride Injection product is a drug-device combination product presented as a ready-to-use sterile solution in 250 mL IV infusion bags, with five strengths containing concentrations of 8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, or 40 mcg/mL epinephrine base.

2. Product Quality

2.1 Drug Substance (Epinephrine)

The drug substance is the R-enantiomer of epinephrine base consistently manufactured in a single crystalline form. The applicant referenced all CMC information on the drug substance to DMF (b) (4) This DMF has been reviewed and found adequate to support other applications. The specification from the drug product manufacturer is consistent with the specification from DMF (b) (4) and the USP monograph, and the NDA includes Certificates of Analysis from both the drug substance and drug product manufacturer for two drug substance batches.

2.2 Drug Product (Epinephrine in sodium chloride)

The drug product is a 250 mL ready-to-use single-dose sterile solution in infusion bags. The inactive ingredients are sodium chloride, hydrochloric acid and/or sodium hydroxide, disodium edetate dihydrate (EDTA), L (+) –tartaric acid, and (b) (4) All excipients are present in acceptable amounts. Oxidative and photo- degradation are significant risks for epinephrine products, and the formulation does not contain an antioxidant; however, it is packaged in an opaque aluminum pouch containing an oxygen scavenger, which protect the drug product from oxidation and light degradation. No other infusion devices are co-packaged with the drug product. Extractable/leachable studies support compatibility of the infusion bags with the epinephrine solution. The tests and acceptance criteria are appropriate to support drug product quality. Stability data support a shelf life of 24 months for the drug product when stored at the recommended storage condition. In-use stability data were provided to support use of the drug product for up to 36 hours after removal from the foil (b) (4)

2.3 Manufacturing

Process: The drug product is manufactured (b) (4) (b) (4) Exhibit batches were manufactured at (b) (4) and (b) (4) (intended commercial) scales using equipment of the same design and operating principles as for the commercial process. The in-

process controls and compatibility studies for product contact equipment were found to be adequate. The manufacturing process overall is adequate.
Facilities: All manufacturing facilities were reviewed, and overall approval for the facilities is recommended based on previous inspection history and manufacturing experience for the manufacturing facilities.

2.4 Biopharmaceutics

The proposed drug product is a ready-to-use diluted solution of epinephrine for intravenous use; therefore, the biopharmaceutics review covered the biowaiver request and scientific bridge, established using a physiochemical comparison to the diluted listed drug. The review concluded that the physicochemical comparison supports the bridge between the listed and the proposed drug products and that an additional *in vivo* bioequivalence (BE) study is not required.

2.5 Microbiology

The microbiology review covered aspects of the drug product manufacturing including the (b) (4) (b) (4) and validation, the container-closure system, the microbiological controls including release and stability test, data, and specifications, environmental monitoring, labeling, and other microbiological aspects. No deficiencies were identified, and the NDA is recommended for approval from the microbiology perspective.

2.6 Quality Labeling

The quality labeling review identified several edits to be recommended in the prescribing information and container labeling. The labeling was recommended for approval after these revisions were implemented.

3. Non-Clinical Pharmacology/Toxicology

Although no new toxicological studies were included in the NDA, the Applicant conducted the following studies: an in vitro red blood cell hemolysis and plasma flocculation study in human blood and a Local Tolerance Study via Intravenous (IV) and Paravenous (PV) administration of NVK019 in New Zealand White Rabbits. These studies were reviewed and by the nonclinical review team and found to be adequate, and the review concluded that all strengths of Epinephrine in 0.9% Sodium Chloride Injection are safe for use in humans from the pharmacology/toxicology perspective.

4. Clinical Pharmacology

Not applicable. No clinical or pharmacokinetic studies have been performed in support of this 505(b)(2) NDA. A scientific bridge to the listed drug is acceptable based on the biopharmaceutics evaluation of the comparative data that were submitted.

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

The product labeling was reviewed and found to be adequate after implementation of minor changes by the Applicant. A request for proprietary name review was not submitted by the Applicant. On February 24th, 2023, the Applicant indicated they plan to submit a Request for Proprietary Name Review in a post approval supplement after the April 22, 2023 action date.

10. Recommended Regulatory Action

NDA 215875 is recommended for approval. The final action of approval or tentative approval will be determined on April 20th, 2023, the conclusion of the 45-day waiting period following the notice of paragraph IV certification that the Applicant has given to the patent holder(s), in accordance with 21 CFR 314.52(b) and (c).

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/

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