CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213407Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 13, 2020
From	Alla Bazini, M.D. Clinical Reviewer Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAMPM)
Through	Rigoberto Roca, M.D. Division Director (acting) Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAMPM)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213407
Applicant	Nexus Pharmaceuticals, Inc.
Date of Submission	June 18, 2019
PDUFA Goal Date	April 18, 2020
Proprietary Name	Emerphed
Established or Proper Name	Ephedrine Sulfate (b) (4) Injection
Dosage Form(s)	Intravenous; 50 mg/10 mL Ephedrine Sulfate, equivalent to 38 mg/10 mL ephedrine base (5 mg/mL, equivalent to 3.8 mg/mL ephedrine base), in a single-dose vial
Applicant Proposed Indication(s)/Population(s)	Ephedrine sulfate (b) (4) injection is an α- and β-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia
Applicant Proposed Dosing Regimen(s)	Bolus 5 to 10 mg as needed, not to exceed 50 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Ephedrine Sulfate injection is an alpha- and beta- adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.
Recommended Dosing Regimen(s)	5 mg to 10 mg administered by intravenous bolus. Additional boluses as needed, not to exceed a total dose of 50 mg. Do not dilute before administration.

Material Reviewed/Consulted: OND Action Package, including:	
Pharmacology/Toxicology	Casandra Cartagena, MS, PhD; Newton Woo, PhD; and Dan Mellon, PhD
OPQ/ONDP/DNDPII/NDPB4	Valerie Amspacher, PharmD; Julia Pinto, PhD
OPQ/ONDP/DNDAPI/NDB2	Lawrence Perez, PhD; Donna Christner, PhD
OPQ/OPMA/DPMAII/PMB6	Yeung Chan, PhD; Yaodong Huang, PhD; Ubrani Venkataram, PhD
OPQ/ONDP/DB/BB1	Sarah Ibrahim, PhD; Hansong Chen, PharmD, PhD, Kelly Kitchens, PhD (formerly)
OPQ/OPMA/DMAI/MAB2	Aditi Das, PhD; Neal Sweeney, PhD
OPQ/OPRO/DRBPMI/RBPMB1	Anika Lalmansingh, PhD
OSE/DMEPA	Cameron Johnson, PharmD; Otto Townsend, PharmD
OPDP	Kuong Lee, RPh, MS
Project Management Staff	Kim Compton, RPh; Matt Sullivan, MS

BB1 = Biophamaceuticals Branch 1
DB = Division of Biopharmaceutics
DMEPA = Division of Medication Error Prevention and Analysis
DNDAPI = Division of New Drug API
DNDPII = Division of New Drug Products II
DMAI = Division of Post-Marketing Activities I
DPMAII = Division of Post-Marketing Activities II
NDB2 = New Drug Branch 2
NDPB4 - New Drug Products Branch 4
OND = Office of New Drugs
ONDP = Office of New Drug Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology
PMB6 = Pharmaceutical Manufacturing Branch 6
OPDP = Office of Prescription Drug Promotion
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology
RBPMB1 = Regulatory & Business Process Management

1. Benefit-Risk Assessment

Ephedrine Sulfate (b) (4) Injection, 5 mg/mL, NDA application is relying on the Agency's previous findings of safety and efficacy of NDA 208289 (Akovaz) for the indication of treatment of clinically important hypotension occurring in the setting of anesthesia. The proposed product label reflects the language in the approved Akovaz product label. Dr. Amelia Luckett's review of NDA 208289 dated April 28, 2016, discusses the details of clinical trials in published literature used to support the safety and efficacy of Akovaz. In her review Dr. Luckett concluded that "Even though ephedrine has been associated with the risk of hypertension and tachycardia, an episode of perioperative hypotension is associated with increased morbidity and mortality, whereupon the use of ephedrine in this situation results in a favorable risk: benefit assessment." (Source: NDA 208289 Clinical Review, page 6). I concur with Dr. Luckett's assessment, which is also applicable to this NDA, as the Applicant requested and was granted a biowaiver that established that their product contains the same active ingredient and (b) (4) sodium chroride as the reference listed drug, Akovaz.

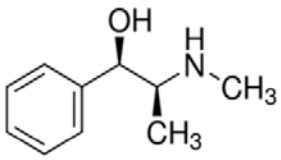
Of note, the proposed product comes in a different strength, 50 mg/10mL, than Akovaz (50 ml/mL), and therefore, does not require dilution prior to administration. The Applicant proposed multiple mitigations strategies, including promotional materials, sales aids, as well as, language on the carton and container to alert physicians regarding the new strength. Drs. Cameron Johnson and Otto Townsend from the Division of Medication Error Prevention and Analysis (DMEPA) as well as Kuong Lee, RPh, MS, from the Office of Prescription Drug Promotion (OPDP) reviewed the proposed materials and provided comments to the Applicant and DAAMPM. I agree with their proposed revisions to the Prescribing Information (PI), the container label and carton labeling to minimize the risk of medication administration errors.

2. Background

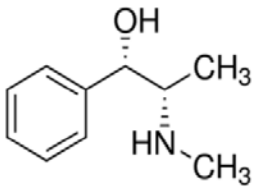
Ephedrine is a sympathomimetic agonist that binds to the α- and ß-adrenergic receptors. In addition to direct interaction with the adrenergic receptors, ephedrine can also have indirect effects by causing the release of endogenous catecholamines and/or by preventing their neuronal reuptake. These effects are manifested clinically as an increase in heart rate and cardiac output, and variable increases in peripheral vasculature resistance, resulting in an increase in systemic blood pressure. There are currently three ephedrine products approved by the Agency: Akovaz® (Ephedrine Sulfate) Injection NDA 208289 held by Avadel Legacy Pharmaceuticals, Corphedra® from Par Sterile Products, LLC (NDA 208943), and Ephedrine Sulfate Injection from Akorn Inc. (NDA 208609). The Applicant is relying on the Agency's previous findings of safety, efficacy, clinical pharmacology, and toxicology information present in the Listed Drug, Akovaz, Prescribing Information. The drug product is (b) (4) the referenced product with the exception that this drug product does not require dilution prior to administration. The Applicant provided adequate justification for any differences in the physiochemical properties between the proposed and the listed drug product.

Ephedrine's chemical structure contains two chiral centers, resulting in two stereoisomers of ephedrine (1R,2S and 1S,2R) and two enantiomers (1R,2R and 1S,2S), known as pseudoephedrine. Diagrammatic representations of these structures are depicted below.

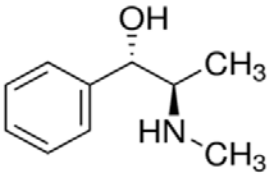
(1R,2S)-(-)Ephedrine



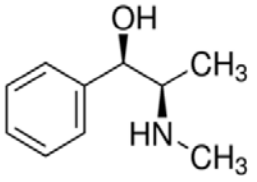
(1S,2S)-(+)Pseudoephedrine



(1S,2R)-(+)Ephedrine



(1R,2R)-(-)Pseudoephedrine



As noted by the team in their reviews of previously approved ephedrine NDAs, the (-)-(1R,2S)–enantiomer of ephedrine cannot convert to (+)-(1R,2S)- enantiomer of ephedrine due to steric hindrance. However, the stereoisomers differ from each other with respect to their relative efficacy. Therefore, it was important that the Applicant establish with as much certainty as possible, the isomeric structure of the ephedrine used in the clinical trials being reported in the published literature being used to support the NDA. With respect to the salt that was used in the clinical trial (i.e., ephedrine sulfate or ephedrine hydrochloride), the Division concluded that either one would be supportive.

Regulatory History

The following table, lists the key regulatory milestones and clinical issues identified during the review of this application:

Meeting/Communication/Date	Event/Key Clinical and Non-Clinical Issues
PIND 128958 Type C Written Responses/November 21, 2016	1. Drug substance and drug product specifications are reasonable, however, Applicant must propose specification for (+) ephedrine drug substance/product and add a test and control for osmolality and chiral purity in the drug product. 2. Twelve months of long-term stability data is necessary at time of NDA submission. 3. If a 505(b)(2) pathways is chosen, Applicant must review existing literature published since approval of listed drug, Akovaz. 4. A 505(b)(2) application to support the proposed indication that relies entirely on non-clinial literature in the public domain will not be adequate to support the NDA due to inadequate information regarding

	mutagenic potential, and impact on reproductive and developmental toxicity available in literature. 5. The NDA submission must provide data to demonstrate blood compatibility and lack of adverse local tissue irritation due to the intravenous (IV) route of administration. 6. Labeling must be consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). 7. If the Applicant is planning on relying on Agency's previous findings of safety and effectiveness of a listed drug, a scientific bridge must be established between their product and the listed drug.
June 18, 2019	NDA received.
August 17, 2019	NDA filed.
Information Request (IR)/June 7, 2019	Requested information regarding 1. Reliance on new published efficacy data 2. Corrections on form 356h 3. Revised annotated package insert in track changes with differences between the Listed Drug and the proposed drug.
Response to IR/June 12, 2019	Applicant confirmed complete reliance on Agency's previous findings of safety and efficacy of Akovaz. Applicant submitted corrected form 356h. Applicant submitted annotated package insert. Applicant stated, "The proposed drug product 's entire label is based on the information mentioned from the Akovaz label, the only difference being that the proposed drug product is a "ready to use" solution for patient administration compared to the RLD that requires prior dilution with sodium chloride before administration."
General Communication/July 3, 2019	Applicant provides clarification that they are seeking regulatory exemption from the Pediatric Research Equity Act (PREA) since the NDA does not contain any new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration.

3. Product Quality

General product quality considerations:

The following summary description of the drug product is reproduced from the OPQ team's review:

For this NDA the drug substance specification complies with the current USP monograph and ICH Q6A guidance. The information on the manufacturer, method of manufacturing, characterization, specification, packaging and stability of ephedrine sulfate is detailed in DMF (b) (4). Nexus Pharmaceuticals has established a retest period of (b) (4) for the drug substance Ephedrine sulfate when stored at (b) (4) which can be granted, based on data in DMF (b) (4) which supports an expiration date of (b) (4).

The drug product is Ephedrine sulfate 5 mg/mL in solution with sodium chloride in (b) (4) mL water. Packaged in a (b) (4) glass vial, (b) (4) (b) (4) aluminum seal with a flip-off cap. A 24-month expiration date is requested and is supported by the stability data. The drug product specification is adequate to assure the identity, strength, quality, purity, and potency of the drug product. The regulatory analytical procedures are appropriate for the intended use, including method validation.

A validated method was used to detect leachables. In a response submitted 27 Feb 2020 the Applicant provided a rigorous, well-performed extractables study. The Applicant will need to reassess the adequacy of the leachables methods based on the additional extractable compounds found in the new study. A leachables study will need to be performed on stability with testing of at least 3 timepoints. Therefore, an adequate leachables study with testing of at least 3 timepoints has not been provided. The following PMC will be sent: To provide assurance on the presence and levels of leachables in the drug product, perform leachables testing on the first commercial stability batch manufactured starting at release and each stability timepoint through to expiry.

Facilities review/inspection:

The following summary description of the drug product is reproduced from the OPQ team's review:

The drug product manufacturing process (b) (4). The drug product is a parenteral injection where the Ephedrine Sulfate in 0.9% Sodium Chloride Injection is packaged in glass vials with 10 mL labeled amount. Scale (b) (4) exhibit batches to (b) (4) commercial manufacturing has been proposed.

The drug product manufacturing facility has experience manufacturing similar liquid formulations. The firm is currently cGMP compliant and their responses to observations identified during the pre-approval inspection (PAI) are acceptable, and the facility is deemed approvable at this time. Similarly, drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is also deemed approvable at this time.

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 213407 are found to be acceptable

Product Quality Microbiology:
The following summary description of the drug product is reproduced from the OPQ team's review:

The submission is recommended for approval on the basis of sterility assurance. No deficiencies were identified.

Biopharmaceutics:
The following summary description of the drug product is reproduced from the OPQ team's review:

The Applicant provided adequate justification for the differences in the physiochemical properties between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), the Agency deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug to be adequate, and a biobridge has been established to the Agency's finding of safety and effectiveness for the Listed Drug (LD). Thus, an in vivo bioavailability (BA)/bioequivalence (BE) bridging study is not needed.

Other notable issues (resolved or outstanding):
I agree with the review team that there are no issues identified that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

Dr. Casandra Cartagena completed the primary pharmacology toxicology review. Drs. Newton Woo (team leader) and R. Daniel Mellon (supervisor) concurred with her recommendation. As discussed in Dr. Cartagena's review, no new nonclinical pharmacology or toxicology studies were submitted or required to support this 505(b)(2) application. The nonclinical review team recommended that the application can be approved because the drug substance and drug product specifications are acceptable, there are no novel excipients in the formations, the toxicological risk assessment for potential leachables is acceptable. Further, they noted that the nonclinical sections of the drug product labeling should be identical to the referenced product labeling. Finally, the team did not recommend any post-marketing studies because the referenced product labeling was recently updated with definitive reproductive and developmental toxicology studies. I concur with the nonclinical team's assessment that there are no nonclinical pharmacology or toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology

The Applicant did not include any new clinical pharmacology information included in this submission, and none was required. There are no clinical pharmacology issues that would preclude approval of this application.

6. Clinical Microbiology

The drug product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical- Efficacy

The Applicant did not conduct any clinical trials in support of the efficacy of their drug product. Instead, the Applicant is relying on the Agency's finding of efficacy for NDA 208289 (Akovaz, ephedrine sulfate). Therefore, there are no efficacy issues identified that would preclude approval of this application.

8. Safety

The Applicant did not conduct any clinical trials in support of the safety of their drug product. Instead, the Applicant is relying on the Agency's finding of safety for NDA 208289 (Akovaz).

The Applicant conducted a review of the published literature starting with 2015, the year of Akvaz NDA first data submission. All literature that provided adverse events was evaluated. There were nine studies that provided adverse events in over 500 women treated for hypotension associated with cesarean anesthesia. There were also four studies of non-cesarean surgery treatment of hypotension associated with anesthesia that identified an additional 162 patients. In addition, there were three case reports identified with possible adverse events from intravenous administration. one-day exposure to ephedrine: two cases of cardiomyopathy and one report of unusual hypertension. No deaths related to ephedrine treatment of hypotension were identified by the Applicant. All adverse events published in literature were consistent with the current Akovaz labeling.

The Applicant also reviewed the FDA Adverse Event Reporting System (FAERS) database from 2015 to 2018 Q3. There were a total of 575 case reports that included ephedrine in the product listing. Of these, 254 were cases considered ephedrine as a suspect drug. Further, 130 of the suspect reports were judged as serious. The Applicant determined that there were no additional safety signals that warrant a change in the approved labeling for Akovaz.

I reviewed the literature publications and the FAERS reports and concluded that no new safety signals were identified, and there were no new safety information that required changes in the package insert.

9. Advisory Committee Meeting

An advisory committee meeting was determined to not be necessary during the review of this application as there were no clinically serious new or unexpected safety concerns identified.

10. Pediatrics

Since the Applicant is referencing NDA 208289, the requirements for pediatric studies under the Pediatric Research Equity Act of 2003 (PREA) are not applicable because the application does not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues.

12. Labeling

Prescribing Information and other labeling (carton and container)

Consultations were obtained from the Division of Medication Error Prevention and Analysis and Office of Prescription Drug Promotion. Their recommendations were incorporated into the product's labeling. Since the Applicant is using NDA 208289 as the reference drug, the proposed label reflects the information in the approved NDA's label.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
None.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
PMC: To provide assurance on the presence and levels of leachables in the drug product, perform leachables testing on the first commercial stability batch manufactured starting at release and each stability timepoint through to expiry.

14. Recommended Comments to the Applicant

None.

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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