CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213994Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Division Director Summary Review for Regulatory Action
Cross-Discipline Team Leader Review
Clinical Review

Date	October 16, 2020
From	Susan Yost, M.D. Martha Van Clief, M.D. Rigoberto Roca, M.D.
NDA Number	NDA 213994
Applicant	Nevakar, Inc.
Date of Submission	December 18, 2019
PDUFA Goal Date	October 18, 2020
Established Name	Ephedrine Sulfate Injection, USP 50mg/10 mL, Prediluted (5mg/mL)
Dosage Form / Strength	Injection for intravenous administration / 5mg/mL
Proposed Indication	Treatment of clinically important hypotension occurring in the setting of anesthesia
Proposed Dosing Regimen	Bolus intravenous injection: 5 to 10 mg as needed, not to exceed 50 mg
Regulatory Action	*Approval*

Material Reviewed/Consulted OND Action Package, including reviews by:	
OPQ	Quality Assessment Team: Sharon Kelly, PhD; Donna Christner, PhD; Cassandra Abellard, BSc; Hansong Chen, PhD; Jizhou Wang, PhD; Bethanie Lee, PhD; Joanne Wang, PhD; Jesse Wells, PhD; Jia Yin, PhD; Anika Lalmansingh, PhD; Valerie Amspacher, PharmD; Julia Pinto, PhD
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DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
OMEPRM = Office of Medication Error Prevention and Risk Management
OPDP=Office of Prescription Drug Promotion
OPEQ = Office of Product Evaluation and Quality
OPQ = Office of Pharmaceutical Quality

1. Benefit-Risk Assessment

This 505(b)(2) application from Nevakar, Inc. for Ephedrine Sulfate, USP, 50 mg/10 mL, prediluted, relies upon the Agency's previous findings of relevant clinical pharmacology, pharmacokinetics, toxicology, safety, and efficacy for the listed drug, Akovaz (ephedrine sulfate injection, USP), NDA 208289. There are no outstanding issues for this application and this application is recommended for approval.

2. Background and Regulatory History

This document will serve as the Division Director Summary Review for Regulatory Action, Cross-Discipline Team Leader Review, and Clinical Review of NDA 213994 for the proposed product, Ephedrine Sulfate Injection, USP 5 mg/mL, ready-to-use formulation.

Ephedrine sulfate is a sympathomimetic amine that directly acts as an agonist at α- and β-adrenergic receptors and indirectly causes the release of norepinephrine from sympathetic neurons. Direct activation of α- and β- adrenergic receptors causes increase in arterial pressure, cardiac output, and peripheral resistance. In addition, indirect adrenergic stimulation occurs by release of norepinephrine from sympathetic nerves. Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Ephedrine sulfate is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

Ephedrine was used as a vasopressor for the treatment of hypotension during anesthesia for decades as a marketed, unapproved product. Ephedrine sulfate was approved for use in the United States on April 29, 2016, (Akovaz, NDA 208289). Since Akovaz is marketed as a 50 mg/mL solution in a 1 mL, it must be diluted to a concentration of 5 mg/mL prior to administration in accordance with the Akovaz package insert. The Applicant proposes a ready-to-use formulation of ephedrine sulfate of 5mg/mL with sodium chloride as the isotonicity agent, therefore further dilution is not required. The composition of the Applicant's proposed formulation compared to the listed drug, Akovaz, is shown below.

Composition of the Drug Product (5mg/mL Ephedrine Sulfate Injection)

Ingredient	Quantity (mg/mL)		
	Akovaz (Undiluted)	Akovaz Diluted to 5 mg/mL with 0.9% Sodium Chloride Injection[a]	Nevakar's Ephedrine Sulfate Injection, USP 5 mg/mL
Ephedrine Sulfate, USP	50.0	5.0	5.0
Sodium Chloride, USP	--	~8.1[b]	9.0
Glacial Acetic Acid, USP	q.s. to pH 4.5-7.0	q.s.[c]	q.s. to pH 4.7
Sodium Hydroxide, NF	q.s. to pH 4.5-7.0	q.s.c	q.s. to pH 4.7
Water for Injection, USP	q.s.	q.s.	q.s.

NF = National Formulary; q.s. = quantity sufficient; USP = United States Pharmacopeia
Reproduced from the Applicant's submission

On March 28, 2018, the Applicant submitted a PIND meeting request for NVK014 (ephedrine sulfate) under IND 138870. A meeting package was submitted May 30, 2018. NVK014 was formulated as a solution of ephedrine sulfate at a concentration of 5 mg/mL intended for intravenous administration. Nevakar proposed to develop and commercialize NVK014 in three presentations: a 10 mL glass vial, (b) (4) The Agency issued a final Written Response (WRO) August 1, 2018 addressing the following topics:

- The selection of the 505(b)(2) pathway regulatory pathway for marketing approval.
- Nevakar's outlined development plan and control strategy for CMC information.
- The requirement for an adequate description of the product's device constituent, intended use environmental, and intended user.
- The requirement for a detailed description of the primary container closure systems.
- The unlikely requirement for additional nonclinical studies to support the safety of NVK014 (ephedrine sulfate).
- The requirement for extractable/leachables data to support the safety of each container closure system configuration you intend to market. Additional nonclinical studies may be required to qualify the safety of any impurity or extractable/leachable that exceed qualification thresholds.
- The required information to support a biowaiver.
- The requirement for a comprehensive risk analysis or plans for a Human Factors (HF) validation study.

It was also noted in the WRO letter that the current label of the reference product and existing literature do not appear to contain adequate information regarding the in vivo mutagenic potential and impact on reproductive and developmental toxicity of ephedrine and therefore nonclinical studies to address these issues may be necessary as postmarketing requirements (PMRs).

On December 18, 2019, Nevakar, Inc. submitted this NDA for Ephedrine Sulfate, 50 mg/10 mL (5 mg/mL) in a single dose vial under the provisions Section 505(b)(2) of the United States Food, Drug and Cosmetic Act (FD&C Act). This application relies upon the Agency's previous findings of safety and effectiveness of the listed drug, Akovaz (ephedrine sulfate) Injection, NDA 208289.

3. Product Quality

The following assessment is reproduced from the Integrated Quality Assessment dated September 16, 2020:

Product Overview:
Ephedrine Sulfate Injection, USP is a clear, colorless, sterile solution filled

into 10 mL glass vials for intravenous administration in the proposed 5 mg/mL strength. Each vial will be packed in a carton.

A shelf-life of 24 months is acceptable when stored at the recommended storage condition of 20°–25° (68°–77° F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

Drug Substance: Adequate
Ephedrine sulfate is manufactured (b) (4) (Adequate, CMC Review #1). The API is the subject of a USP monograph. The supplier specification meets the monograph requirements. Additional testing by (b) (4) includes residual solvents (b) (4) and elemental impurities. They have provided the sponsor with an Elemental Risk Assessment which supports elimination of this testing. The specification includes a test for enantiomeric purity (NLT (b) (4)%) because the ephedrine sulfate manufactured by (b) (4) is predominantly the (-)-ephedrine sulfate. The non-USP methods were fully validated by (b) (4) and they have provided the reports to (b) (4), the drug product manufacturer. (b) (4) performed method verification which includes: system suitability, specificity, method precision, and results comparison to (b) (4) Certificate of Analysis.

Representative batch analysis data is provided for the two batches used or registration and stability of the drug product. The data conforms to specification (assay NLT (b) (4)%. Total impurities NMT (b) (4)%, Chiral purity NLT (b) (4)%). The holder of DMF (b) (4) has established a (b) (4) month retest date for the drug substance based on currently available stability results included in the DMF

Drug Product: Adequate
The sponsor has manufactured three (3) registration batches of drug product. All the excipients (Sodium chloride, sodium hydroxide and/or acetic acid) are USP grade. The quality of the drug product has been adequately controlled as per official USP monograph, USP General Chapters, ICH guidelines and internal data trends.
The long term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C / 75 ± 5% RH) stability storage conditions as well as the photo stability and Freeze/Thaw stress stability studies justified a shelf-life of 24 months when the drug product is stored at the recommended storage condition of 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).
The sponsor has performed adequate extractables and leachables studies to demonstrate the suitability of the primary packaging system.

Labeling: Adequate
No additional comments.

Manufacturing: Adequate
The manufacturing process consists of (b) (4) The drug product is supplied in a 10 mL USP (b) (4) clear glass vial with a (b) (4) stopper and an aluminum seal. The drug product manufacturer is acceptable after PAI. All other facilities are acceptable.

Biopharmaceutics: Adequate
In this NDA submission, Nevakar submitted the information based on Agency's response dated August 1, 2018, to support a biowaiver request for the proposed product. Biopharmaceutics assessment is focused on the biowaiver request.

The formulation of the proposed drug product and the post-dilution LD is similar, except a small difference in the amount of sodium chloride, which is not expected to affect the bioavailability of the proposed drug product. The provided physicochemical comparison data showed similarity in pH and osmolality between the post-dilution LD and the proposed drug product. Per CFR 320.24(b)(6), A biobridge between the LD (Akovaz, N 208289) and proposed drug product has been established.

Microbiology: Adequate
The integrity of the proposed container closure system was adequately validated. (b) (4)

The release specifications contain adequate controls to assure microbiological control of the subject drug product.

Recommendation of Quality Team:
All CMC disciplines recommend approval.

We concur with the assessment of the quality review team.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical pharmacology or toxicology studies submitted in support of this NDA application. The pharmacology/toxiciology reviewer, Casandra Cartagena, MS PhD, noted the following summary in her review dated October 9, 2020:

> The drug product differs in osmolality, pH, and does not have to be diluted as compared to the reference product. Blood compatibility (hemolysis, flocculation of proteins, platelet activation) and local irritation studies are generally conducted to support safety of a change in formulation as per Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route. Because the drug product has a different pH and osmolality compared to the LD, these aspects of safety were addressed in the NDA submission and were deemed acceptable.

The following is adapted from Dr. Cartagena' review regarding a drug product degradant.

> The Applicant did not provide a specification for d-ephedrine sulfate in the drug product. However, the Applicant provided testing for the d-ephedrine at 18 months and none was detected. Therefore, it appears that the degradant was adequately controlled at the level of the drug substance (refer to CMC review for further details).

Regarding the reproductive and developmental toxicology assessment for this drug product the following is adapted from Dr. Cartagena's review.

> There were no reproductive and developmental toxicology studies with ephedrine sulfate submitted in this NDA and the Applicant did not submit literature to address these standard requirements. However, the pregnancy section of the Akovaz product label was recently updated and the Applicant is relying upon the data in the Akovaz product labeling.

The drug product differs in osmolality compared to the reference product. The following is reproduced from Dr. Cartagena's review:

> Initially, the Applicant proposed an osmolality specification of (b) (4) mOsm/kg. In the Day 74 letter the Applicant was asked to justify the safety of the proposed osmolality by providing a blood compatibility evaluation (hemolysis, flocculation of proteins, platelet activation) and local irritation study as per Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route. Subsequently, the Applicant proposed an osmolality specification of (b) (4) mOsm/kg. This specification is within the range of the reference product at the lower bound but is about 7% greater than the reference product

> at the upper bound. The Applicant provided a justification for safety including that the difference is 6.7% and osmolality range proposed is similar to the osmolality for blood (per Applicant blood osmolality is 285-310 mOsm/kg). In addition, the Applicant references literature sources where in small clinical studies administration of higher osmolality solutions did not result in local toxicity (Berg 2002 and Holcroft 1987) .

After review of the literature references submitted by the Applicant, discussion with the clinical review team, and review of additional supportive literature, Dr. Cartagena concludes that the difference between the proposed osmolality specification and that of other infused solutions is comparable.

Dr. Cartagena's final assessment is reproduced here:

> Taken together, the proposed upper end of osmolality range is within whole blood osmolality levels and other commonly used IV solutions, the dosing regimen is an acute bolus dose, and that administration of ephedrine will likely be diluted given the dead space between the injection port and the catheter injection site, the proposed difference in osmolality between the drug product and the reference product is unlikely to raise any safety concerns.

The pharmacology/toxicology team concluded that the application may be approved.

We concur with the assessment of the pharmacology/toxicology team.

5. Clinical Pharmacology

There were no pharmacokinetic or ADME studies with the proposed drug product submitted in this NDA. The Applicant is relying upon the data in the referenced product labeling. The Applicant relying on the FDA's previous findings of safety and efficacy for Akovaz, the listed drug, as the proposed indication, route of administration and dosing regimen are the same.

The Applicant requested a biowaiver in the NDA submission. The biopharmacology reviewer provided the following clarification of the bridge in an amendment to the 505(b)(2) form for the 505(b)(2) Committee:

> LD bridge:
> - A bridge between the relied-upon listed drug (LD), Akovaz (NDA 208289), and proposed drug product has been established under 21 CFR 320.24(b)(6).
> - Both the LD and proposed drug product are for Intravenous Injection. The proposed drug product contains the same concentration of active ingredient as the diluted LD. Although the LD and proposed drug product have slightly different concentrations of inactive ingredient, the disposition of the drug following intravenous injection of solution is not expected to be affected by this difference.

- The small differences in osmolality between the proposed product and the LD are not expected to affect bioavailability. The two products otherwise have comparable physicochemical properties, including pH.

Literature bridge:
The Applicant provided two clinical study publications describing different drug products with osmolalities significantly greater than that of the proposed product to justify the safety of the osmolality difference of the upper limits between the proposed product and the LD. The clinical studies report a lack of adverse effects such thrombophlebitis or vascular irritation following infusion of solutions with higher osmolality than the proposed product. Importantly, the osmolality range proposed for Nevakar's proposed product is similar to the osmolality reported for blood (285-310 mOsm/Kg) in USP general chapter <USP 785>. These data are deemed adequate to justify the conclusion that the difference in osmolality is not expected to alter the safety profile of the proposed drug compared to the LD.

6. Clinical Microbiology

Ephedrine sulfate injection, USP, 5 mg/mL, is not a therapeutic antimicrobial, therefore clinical microbiology data were neither required or submitted.

7. Clinical/Statistical- Efficacy

The Applicant relied upon the Agency's previous findings of effectiveness for the listed drug, Akovaz (ephedrine sulfate injection, USP), manufactured by Flamel Ireland Limited (NDA 208289), approved on April 29, 2016. Therefore, Section 7 is not relevant to this 505(b)(2) application.

8. Safety

The Applicant relied upon the Agency's previous findings of safety and effectiveness for the listed drug, Akovaz (ephedrine sulfate injection, USP), manufactured by Flamel Ireland Limited (NDA 208289), approved on April 29, 2016. Therefore, this section will briefly discuss the safety updates submitted with the initial submission of this NDA, the Applicant's response to the 74-Day Letter, and the 120-Day Safety Update Report.

The Applicant conducted a review of the literature subsequent to the approval of an updated package insert for the listed drug, (Akovaz PI, August 2018) to September 16, 2019. Following a request from the Agency in the 74-day letter, they included a review of the literature from the time of approval of Akovaz to August 2018. In review of this clinical data, there were no new safety findings that may affect labeling. In addition, the Applicant submitted a 120-Day Safety Update Report that did not reveal any new safety findings.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting**.**

10. Pediatrics

This drug product, ephedrine sulfate injection 5mg/mL, does not include a new active ingredient, nor propose a new indication, new dosage form, new dosing, regimen, or new route of administration. Therefore, this application does not trigger PREA and no pediatric studies are required.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues for this application.

12. Labeling

The proposed labeling for Ephedrine Sulfate Injection, USP, 50 mg/10mL, (5mg/mL) prediluted, is based on the currently approved United States Prescribing Information for the listed drug, Akovaz (NDA 208289). Therefore, there were minimal labeling modifications.

The following changes were made to the Highlight Section of the label.

- Dosage and Administration:
  - Removed: Dilute before administration.
  - Added: Ready to Use formulation. Do not dilute.
- Dosage Forms and Strengths:
  - Removed: Ephedrine sulfate injection is available as a single-dose 1 mL vial that contains 50 mg/mL ephedrine sulfate, equivalent to 38 mg ephedrine base.
  - Added: Injection: 5mg/mL, ephedrine sulfate in a ready-to-use single dose, 10 mL vial (50 mg/10mL), equivalent to 38 mg ephedrine base.

The following changes were made to the Full Prescribing Information of the label:

- Section 2.1 General Dosage and Administration Instructions:
  - Added: Ready to Use formulation. Do not dilute.
  - Deleted: Ephedrine sulfate injection must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.
- Section 2.3 Prepare a 5 mg/mL Solution for Bolus Intravenous Administration, from Akovaz, label was deleted.

Excela Pharma (Akovaz) submitted a supplement new drug application October 26, 2018 to address Postmarketing Requirements for additional nonclinical studies and provide changes to the Use in Special Populations and Nonclinical Toxicology sections of the package insert. The Prior Approval supplement was approved April 8, 2020 and the nonclinical PMRs were fulfilled. The Applicant's proposed label was modified during the review cycle to include all the changes to the Akovaz label based upon the April 8, 2020 approval of the Prior Approval supplement.

DMEPA conducted a review of the container label and carton labeling to identify areas of vulnerability that may lead to medication errors. Their recommendation to the Applicant can be found in the DMEPA review by Cameron Johnson, PharmD, dated May 20, 2020. On August 19, 2020, a Memorandum Review of revised label and labeling was completed by Cameron Johnson, PharmD (DMEPA) with the following conclusion:

> The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

13. Postmarketing Recommendations

There are no REMS, PMRs, or PMCs required for this application.

14. Recommended Comments to the Applicant

There are no recommended comments to the Applicant.

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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10/16/2020 12:21:40 PM

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