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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	213994
Supporting document/s:	1, 8, 12, 13, 14
Applicant's letter date:	December 18, 2019
CDER stamp date:	December 18, 2019; June 29, 2020; August 31, 2020; September 8, 2020; October 6, 2020
Product:	Ephedrine sulphate injection
Indication:	Clinically important hypertension in the setting of anesthesia
Applicant:	Nevakar Inc.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Casandra Cartagena, MS PhD
Supervisor/Team Leader:	R. Daniel Mellon, PhD/ Newton Woo, PhD
Clinical Division Director:	Rigoberto Roca, MD (Acting)
Project Manager:	Kimberly Compton

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

The Applicant is submitting NDA 213994 via the 505(b)(2) regulatory pathway with Akovaz (NDA 208289) as the relied-upon listed drug (LD). The proposed product is not a generic product because, unlike the reference product, it does not require dilution before use. The Applicant is relying on the Agency's previous findings of safety and the relevant pharmacology, pharmacokinetics, and toxicology information in the label of the LD.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical pharmacology or toxicology studies submitted in support of this NDA application. 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 Applicant initially proposed drug substance and drug product impurity specifications for the isomer d-ephedrine sulfate above the qualifying threshold but has agreed to modify the specifications to NMT (b) (4) % in the drug substance, which is below the qualification thresholds per ICH Q3A(R2). There are no outstanding nonclinical safety issues with the drug product formulation or container closure system.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 213994 may be approved.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant with the changes proposed by this Reviewer and the rationale for the proposed changes. The labeling recommendations below have not been discussed with the entire review team or the Applicant. The reader is referred to the final action letter for the final drug product

labeling. The nonclinical sections of the final drug product labeling is identical to the most recently approved Akovaz drug product labeling.

Table 1. Labeling Review

Applicant's Proposed Labeling	Reviewer's Proposed Changes	Rationale for Changes
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Risk Summary [redacted (b) (4)] However, there are clinical considerations [*see Clinical Considerations*]. [redacted (b) (4)] In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical Considerations *Fetal/Neonatal Adverse Reactions* Cases of potential metabolic acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe umbilical artery pH of ≤7.2 at the time of delivery [*see Clinical Pharmacology*	Risk Summary Available data from randomized studies, case series, and reports of ephedrine sulfate use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, there are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies, decreased fetal survival and fetal body weights were observed in the presence of maternal toxicity after normotensive pregnant rats were administered 60 mg/kg intravenous ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg/day). No malformations or embryofetal adverse effects were observed when pregnant rats or rabbits were treated with intravenous bolus doses of ephedrine sulfate during organogenesis at doses 1.9 and 7.7 times the MRHD, respectively *[See data]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse	See the clinical review and/or the MHT review for human data labeling recommendations. These data reflect the most recently approved labeling from the relied-upon listed drug (LD).

12.3]. Monitoring of the newborn for signs and symptoms of metabolic acidosis may be required. Monitoring of infant's acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.	outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data *Animal Data* Decreased fetal body weights were observed when pregnant rats were administered intravenous bolus doses of 60 mg/kg ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6-17. This dose was associated with evidence of maternal toxicity (decreased body weight of dams and abnormal head movements). No malformations or fetal deaths were noted at this dose. No effects on fetal body weight were noted at 10 mg/kg (1.9 times the MRHD of 50 mg). No evidence of malformations or embryo-fetal toxicity were noted in pregnant rabbits administered intravenous bolus doses up to 20 mg/kg ephedrine sulfate (7.7 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6-20. This dose was associated with expected pharmacological maternal effects (increased respiration rate, dilated pupils, piloerection). Decreased fetal survival and body weights in the presence	

	of maternal toxicity (increased mortality) were noted when pregnant dams were administered intravenous bolus doses of 60 mg/kg epinephrine sulfate (approximately 12 times the MRHD based on body surface area) from GD 6 through Lactation Day 20. No adverse effects were noted at 10 mg/kg (1.9 times the MRHD).	
8.4 Pediatric Use Safety and effectiveness in pediatric patients have not been established.	**8.4 Pediatric Use** Safety and effectiveness in pediatric patients have not been established. Animal Toxicity Data In a study in which juvenile rats were administered intravenous bolus doses of 2, 10, or 60 mg/kg ephedrine sulfate daily from Postnatal Day 35 to 56, an increased incidence of mortality was noted at the high dose of 60 mg/kg. The no-adverse-effect level was 10 mg/kg (approximately 1.9 times a maximum daily dose of 50 mg in a 60 kg person based on body surface area).	Animal Toxicity Data section was added to match the label of the LD.
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** 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. Pressor effects by direct alpha- and beta-adrenergic	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** 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. Pressor effects by direct alpha- and beta-adrenergic	No changes necessary. Final labeling is identical to the most recently approved labeling of the LD.

receptor activation are mediated by increases in arterial pressures, cardiac output, and peripheral resistance. Indirect adrenergic stimulation is caused by norepinephrine release from sympathetic nerves.	receptor activation are mediated by increases in arterial pressures, cardiac output, and peripheral resistance. Indirect adrenergic stimulation is caused by norepinephrine release from sympathetic nerves.	
12.2 Pharmacodynamics	**12.2 Pharmacodynamics**	
Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Stimulation of the α-adrenergic receptors of smooth muscle cells in the bladder base may increase the resistance to the outflow of urine. Activation of β-adrenergic receptors in the lungs promotes bronchodilation.	Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Stimulation of the α-adrenergic receptors of smooth muscle cells in the bladder base may increase the resistance to the outflow of urine. Activation of β-adrenergic receptors in the lungs promotes bronchodilation.	
The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, β-2 adrenoceptor-mediated vasoconstriction, and β-2 adrenoceptor-mediated vasodilatation. Stimulation of the β-1 adrenoceptors results in positive inotrope and chronotrope action.	The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, β-2 adrenoceptor-mediated vasoconstriction, and β-2 adrenoceptor-mediated vasodilatation. Stimulation of the β-1 adrenoceptors results in positive inotrope and chronotrope action.	
Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration [*see Warnings and Precautions 5.2*].	Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration [*see Warnings and Precautions 5.2*].	

12.3 Pharmacokinetics Publications studying pharmacokinetics of oral administration of (-)-ephedrine support that (-)-ephedrine is metabolized into norephedrine. However, the metabolism pathway is unknown. Both the parent drug and the metabolite are excreted in urine. Limited data after IV administration of ephedrine support similar observations of urinary excretion of drug and metabolite. The plasma elimination half-life of ephedrine following oral administration was about 6 hours. Ephedrine crosses the placental barrier [*see Use in Specific Populations 8.1*].	**12.3 Pharmacokinetics** Publications studying pharmacokinetics of oral administration of (-)-ephedrine support that (-)-ephedrine is metabolized into norephedrine. However, the metabolism pathway is unknown. Both the parent drug and the metabolite are excreted in urine. Limited data after IV administration of ephedrine support similar observations of urinary excretion of drug and metabolite. The plasma elimination half-life of ephedrine following oral administration was about 6 hours. Ephedrine crosses the placental barrier [*see Use in Specific Populations 8.1*].	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u>: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to 10 mg/kg/day and 27 mg/kg/day (approximately 2 times and 3 times the maximum human	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u>: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to 10 mg/kg/day and 27 mg/kg/day (approximately 2 times and 3 times the maximum human	These data reflect the most recently approved labeling from the LD.

recommended dose on a mg/m^2 basis, respectively). Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay, the in vitro mouse lymphoma assay, the in vitro sister chromatid exchange, the in vitro chromosomal aberration assay, and the in vivo rat bone marrow micronucleus assay. Impairment of Fertility: (b) (4)	recommended dose on a mg/m^2 basis, respectively). Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay, the in vitro mouse lymphoma assay, the in vitro sister chromatid exchange, the in vitro chromosomal aberration assay, and the in vivo rat bone marrow micronucleus assay. Impairment of Fertility: (b) (4) There was no impact on fertility or early embryonic development in a study in which male rats were administered intravenous bolus doses of 0, 2, 10, or 60 mg/kg ephedrine sulfate (up to 12 times the maximum recommended human dose of 50 mg based on body surface area) for 28 days prior to mating and through gestation and females were treated for 14 days prior to mating through Gestation Day 7.	

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 134-72-5

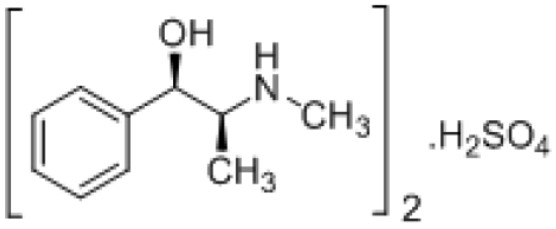
Generic Name: ephedrine sulfate

Code Name: n/a

Chemical Name: benzenemethanol, α-[1-(methylamino) ethyl]-, [R-(R*, S*)]-, sulfate (2,1)(salt)

Molecular Formula/Molecular Weight: $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$/428.54

Structure or Biochemical Description



Established Pharmacologic Class: alpha and beta adrenergic agonist and norepinephrine releasing agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 2. Referenced NDA, IND, and DMFs

Application	Product Name	Submitter	Division	Status
NDA-208289	Akovaz	AVADEL LEGACY PHARMACEUTICALS LLC	DAAP	Approved, 505(b)(2) relied-upon listed drug
PIND-138870	Ephedrine Sulfate Injection, USP	NEVAKAR INC	DAAP	Presubmission
DMF- (b) (4)	Ephedrine sulfate drug substance	(b) (4)	DRM	Active
DMF- (b) (4)	Stopper		DRM	Active
DMF- (b) (4)	Stopper		DRM	Active
DMF- (b) (4)	Vial		DRM	Active

2.3 Drug Formulation

The composition of the Applicant's ephedrine sulfate injection differs from the reference product in that it is ready to infuse and does not require further dilution whereas the reference product is designed to be diluted 10x before use.

Table 3. Composition of the Drug Product (5 mg/mL ephedrine sulfate injection)

Per the Applicant's submission:

Ingredient	% w/v	Quantity/mL	Quantity/vial (10 mL)	Pharmaceutical Function
Ephedrine sulfate, USP	0.5	5.0 mg	50.0 mg (equivalent to 38 mg of ephedrine base)	Active
Sodium chloride, USP	0.9	9.0 mg	90.0 mg	(b) (4)
(b) (4) Glacial acetic acid, USP Sodium hydroxide, NF	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	pH adjuster(s) (b) (4)
Water for Injection, USP	q.s. to 1.0 mL	q.s.	q.s. to 10 mL	Vehicle
Total volume	NA	1 mL	10.0 mL	NA

q.s. = quantity sufficient; NA = not applicable; NF = National Formulary; USP = United States Pharmacopoeia

The maximum daily dose of ephedrine sulfate is 50 mg/day.

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation. All of the excipients are listed in the FDA Inactive Ingredients Database (IID) and are used in FDA-approved drug products at levels greater than those in the proposed ephedrine sulfate drug product when taking into consideration the concentration and maximum daily intake.

Table 4. Excipients Included in the Drug Product and Qualification Status

Ingredients	Function	Amount (mg/mL)	Maximum exposure (mg/day)	Acceptable? (Rationale)
Glacial acetic acid	pH adjustment	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	Yes (IID)
Sodium Chloride	(b) (4)	9.0	90.0	Yes (IID)
Sodium hydroxide	pH adjustment	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	Yes (IID)

Water for injection	Vehicle	q.s.	q.s. to 10 mL	Yes (IID)

IID: FDA Inactive Ingredient Database

2.5 Comments on Impurities/Degradants of Concern

The Applicant is referencing [redacted] for ephedrine sulfate drug substance. The drug substance impurity specifications are presented in the table below. The Applicant has set a specification of NMT [redacted]% for any unspecified individual impurity, which is deemed acceptable. In their initial submission the Applicant proposed a drug substance specification of NMT [redacted]% for d-ephedrine sulfate, which exceeds ICH Q3A(R2) qualification threshold. Following an information request the Applicant agreed to modify the specification for d-ephedrine sulfate in the drug substance to NMT [redacted]%, which is acceptable.

Table 5. Drug Substance Impurities and Qualification Status

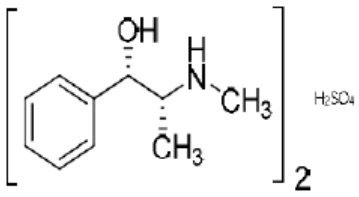
Impurity/ Degradants	Structure	Proposed Specification	Acceptability and Justification
d-Ephedrine sulfate / (1S,2R)-2-(methylamino)-1-phenylpropan-1-ol sulfate		NMT [redacted]%	Acceptable. Below ICH Q3A(R2) qualification threshold.
[redacted]		NMT [redacted]%	Acceptable. Below ICH Q3A(R2) qualification threshold.
Any unspecified impurity	N/A	NMT [redacted]%	Acceptable. Below ICH Q3A(R2) qualification threshold.

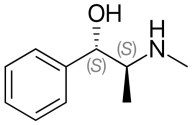
Table 6. Residual Solvents and Qualification Status

Residual Solvent	Specification	Acceptability and Justification
[redacted]	NMT [redacted] ppm	Acceptable. Below ICH Q3C.
	NMT [redacted] ppm	Acceptable. Below ICH Q3C.
	NMT [redacted] pm	Acceptable. Below ICH Q3C.

Drug Product Degradants

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

Table 7. Drug Products Impurities and Qualification Status

Impurity/ Degradants	Structure	Proposed Specification	Acceptability and Justification
Pseudoephedrine		NMT (b) (4) %	Acceptable. Below ICH Q3B(R2) qualification threshold.
Any unspecified impurity		NMT (b) (4) %	Acceptable. Below ICH Q3B(R2) qualification threshold.

The Applicant provided stability testing data for 3, 6, 9, 12, and 18 months at ambient temperatures (25C/60% RH) in both the upright and inverted positioning. No impurities or degradants were observed. The Applicant also provided stability testing for 12 and 18 months at ambient temperatures in the inverted position specifically assessing chiral degradants. No d-ephedrine, l-pseudoephedrine, or d-pseudoephedrine were observed.

There are no issues with impurities as drug substance impurities, residual solvents, and drug product degradants were below respective ICH thresholds.

Table 8. Constituents of the Container Closure System

Per the Applicant's submission:

Component	Description	OsoBio Item No.	Vendor Item No.	Supplier	Supplier Address
Stopper	(b) (4)				
Vial					
Seal					

[a] DMF not required as component is not in contact with drug product

Extractable Studies

(b) (4)

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2.6 Proposed Clinical Population and Dosing Regimen

The Applicant plans to pursue the indication that is approved for the reference product Akovaz, which is clinically important hypertension in the setting of anesthesia.

The Applicant proposes the following dosing regimen, which is the same as the reference product except that the reference product requires dilution before administration.

DOSAGE AND ADMINISTRATION

- Ephedrine sulfate in 0.9% sodium chloride injection, 5mg/mL, (50mg/Vial) (equivalent to 38 mg ephedrine base) is injected intravenously as a bolus. (2) ***No dilution is required prior to administration***.
- Bolus intravenous injection: 5 to 10 mg as needed, not to exceed 50 mg. (2)

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency's previous findings of safety and efficacy to Akovaz (NDA 208289).

The Applicant submitted a PIND meeting package May 30, 2018 under IND 138870. Written responses were conveyed to the Applicant August 1, 2018. Excerpts of the nonclinical comments that were communicated to the Applicant are shown below:

Question 7
NVK014 will contain 5 mg/mL ephedrine sulfate, with sodium chloride (b) (4) *The composition of the Nevakar product will be similar to that of the RLD diluted with 0.9% sodium chloride injection for administration, in accordance with its prescribing information. Furthermore, pH and osmolality of NVK014 will be similar to the diluted RLD. Does the Agency agree that no additional in vitro or in vivo nonclinical toxicology studies are required to support an NDA 505(b)(2) application for NVK014?*

FDA Response to Question 7
Yes, we agree that no additional nonclinical studies are likely required to support the safety of ephedrine sulfate in a NDA 505(b)(2) application for NVK014. However, we note that the current label of the referenced 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). Final determination regarding whether PMRs will be required can only be provided upon detailed review of the referenced literature studies.

Note that extractables/leachables data must be provided 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 (see Additional Nonclinical Comments). For example, isomers of (-)-ephedrine are impurities (e.g., (+) ephedrine isomer). These impurities must be qualified if any exceed qualification thresholds.

Additional boilerplate language regarding nonclinical recommendations for their submission was also communicated to the Applicant.

The Applicant submitted a justification for why the difference in osmolality between their drug product and the reference product did not require additional nonclinical assessment. The justification referenced several FDA-approved drug products. On August 25, 2020 the Division met with the Applicant via teleconference to convey to them that if they chose to reference additional FDA-approved drug products as part of the 505(b)(2) regulatory pathway they must also provide a scientific bridge to each of the references drug products and submit adequate patent certification. As a result, the Applicant has resubmitted a scientific justification that did not rely on other FDA approved products but instead submitted two clinical literature references (see Section 10 Special Toxicology Studies).

3 Studies Submitted

There were no nonclinical studies submitted in this NDA.

4 Pharmacology

There were no primary, secondary, or safety pharmacology studies with ephedrine sulfate submitted in this NDA. The Applicant is relying upon the data in the referenced product labeling.

5 Pharmacokinetics/ADME/Toxicokinetics

There were no pharmacokinetic, ADME, or toxicokinetic studies/data with ephedrine sulfate submitted in this NDA. The Applicant is relying upon the data in the referenced product labeling.

6 General Toxicology

There were no general toxicology studies with ephedrine sulfate submitted in this NDA. The Applicant is relying upon the data in the referenced product labeling.

7 Genetic Toxicology

There were no genetic toxicology studies with ephedrine sulfate submitted in this NDA. The Applicant is relying upon the data in the referenced product labeling. The following information on the genetic toxicology of ephedrine sulfate is from the referenced Akovaz label:

> Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay, the in vitro mouse lymphoma assay, the in vitro sister chromatid exchange, the in

vitro chromosomal aberration assay, and the in vivo rat bone marrow micronucleus assay.

8 Carcinogenicity

As the proposed drug product is for acute use, a carcinogenicity evaluation with ephedrine sulfate is not required. The Applicant is relying upon the data in the referenced product labeling. The following information on carcinogenicity of ephedrine sulfate is from the referenced Akovaz label:

Carcinogenesis: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to 10 mg/kg/day and 27 mg/kg/day (approximately 2 times and 3 times the maximum human recommended dose on a mg/m^2 basis, respectively).

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with ephedrine sulfate submitted in this NDA. The Applicant did not submit literature to address these standard requirements. The Applicant is relying upon the data in the referenced product labeling.

The following information on the reproductive and developmental toxicology of ephedrine sulfate is from the recently updated pregnancy section of the referenced product Akovaz:

Risk Summary

Available data from randomized studies, case series, and reports of ephedrine sulfate use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, there are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies, decreased fetal survival and fetal body weights were observed in the presence of maternal toxicity after normotensive pregnant rats were administered 60 mg/kg intravenous ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg/day). No malformations or embryofetal adverse effects were observed when pregnant rats or rabbits were treated with intravenous bolus doses of ephedrine sulfate during organogenesis at doses 1.9 and 7.7 times the MRHD, respectively *[See data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Cases of potential metabolic acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe umbilical artery pH of ≤7.2 at the time of delivery *[see Clinical Pharmacology 12.3]*. Monitoring of the newborn for signs and symptoms of metabolic acidosis may be required. Monitoring of infant's acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.

Data

Animal Data

Decreased fetal body weights were observed when pregnant rats were administered intravenous bolus doses of 60 mg/kg ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6-17. This dose was associated with evidence of maternal toxicity (decreased body weight of dams and abnormal head movements). No malformations or fetal deaths were noted at this dose. No effects on fetal body weight were noted at 10 mg/kg (1.9 times the MRHD of 50 mg).

No evidence of malformations or embryo-fetal toxicity were noted in pregnant rabbits administered intravenous bolus doses up to 20 mg/kg ephedrine sulfate (7.7 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6-20. This dose was associated with expected pharmacological maternal effects (increased respiration rate, dilated pupils, piloerection).

Decreased fetal survival and body weights in the presence of maternal toxicity (increased mortality) were noted when pregnant dams were administered intravenous bolus doses of 60 mg/kg epinephrine sulfate (approximately 12 times the MRHD based on body surface area) from GD 6 through Lactation Day 20. No adverse effects were noted at 10 mg/kg (1.9 times the MRHD).

The following information on the impairment of fertility of ephedrine sulfate is from the recently updated nonclinical toxicology section of the referenced product Akovaz:

Impairment of Fertility: There was no impact on fertility or early embryonic development in a study in which male rats were administered intravenous bolus doses of 0, 2, 10, or 60 mg/kg ephedrine sulfate (up to 12 times the maximum recommended human dose of 50 mg based on body surface area) for 28 days prior to mating and through gestation and females were treated for 14 days prior to mating through Gestation Day 7.

At the time of the preIND meeting it was noted that if adequate data were not present in the referenced drug product labeling or identified in the literature, these studies may be required to be completed post marketing. However, the referenced product labeling has been updated to include data from developmental and reproductive toxicology studies

and therefore PMRs will not be required and data from the referenced product labeling are included in this drug product label.

10 Special Toxicology Studies

Local Tolerance

There were no special toxicology studies with ephedrine sulfate submitted in this NDA. The drug product differs in osmolality compared to the reference product. 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 (Holcroft 1987, Berg 2002).

Although this Reviewer along with the Medical review team agrees that the clinical studies provided by the Applicant provide some evidence of safety for intravenous administration of higher osmolality solutions, these data are limited given the low sample size. Upon further review of the available literature, this Reviewer agrees that the difference between the proposed osmolality specification and that of other infused solutions (e.g., blood) is comparable. In support of this, a study that evaluated the metabolic load of stored blood measured several parameters from aliquots of stored blood used for clinical transfusions to infants and reported a blood osmolality range of 308-320 mOsm/kg (Ratcliffe 1986). In this case, the proposed osmolality is within 2% of this standard treatment. In another publication, osmolality of whole blood samples collected from hospital patients were reported to have a range between 252 to 365 mOsm/kg with a mean of 288.9 mOsm/kg (Rocks 1986). It is also noted that other intravenous solutions that are hypertonic are routinely administered intravenously, e.g., 3% NaCl (1030 mOsm/L) is used to treat severe, critical hyponatremia and dextrose solutions (406 mOsmol/L) are used to treat hypovolemia. Another consideration for local safety is the rate of infusion of the solution. Studies in rabbits indicated that higher osmolality solutions were better tolerated with acute dosing compared with longer infusions (Kuwahara 1998). In this study a hyperosmolality solution was infused through a catheter into an ear vein at infusion durations of 8, 12, or 24 hours. Rabbits were necropsied 20-24 hours after the end of infusion and sections were stained with hematoxylin and eosin and microscopic examination was performed blindly. Infusion of an 814 mOsm/kg solution for 8 hours resulted in one incidence of minimal loss of endothelial cells and edema, with no incidences of inflammatory cell infiltration or thrombus. In contrast infusion of the same solution at 12 or 24 hours results in several

incidences of minimal to moderate loss of venous endothelia cells, inflammatory cell infiltration, edema, and a single incidence of minimal thrombus. The study concluded that hypertonic solutions should be infused at the highest rate clinically feasible as the data demonstrated that increasing infusion rates of hyperosmolality solutions was associated with lower incidences of microscopic findings and phlebitis. In the case of the proposed drug product, ephedrine is administered as a bolus dose up to a maximum volume of 10 mL. Finally, it was pointed out by the clinical review team that standard practice for bolus I.V. doses are generally administered in conjunction with fluids such as saline or Ringer's solution such that the small difference in osmolality between ephedrine is likely to be further diluted with the solution present between the injection port and the blood vessel at the site of injection. 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.

Nonclinical Safety of Pediatric Population

The following information on juvenile animal toxicology of ephedrine sulfate is from the pediatric use of the referenced product Akovaz:

Animal Toxicity Data
In a study in which juvenile rats were administered intravenous bolus doses of 2, 10, or 60 mg/kg ephedrine sulfate daily from Postnatal Day 35 to 56, an increased incidence of mortality was noted at the high dose of 60 mg/kg. The no-adverse-effect level was 10 mg/kg (approximately 1.9 times a maximum daily dose of 50 mg in a 60 kg person based on body surface area).

The referenced drug product labeling has been updated with juvenile animal data recently and therefore these data are included for this drug product labeling.

11 Integrated Summary and Safety Evaluation

In their initial submission the Applicant proposed a drug substance specification of NMT (b) (4)% for d-ephedrine sulfate, which exceeds the qualifying threshold and did not propose specification for d-ephedrine sulfate in the drug product. Following an information request the Applicant agreed to modify the specification for d-ephedrine sulfate in the drug substance to NMT (b) (4)% which does not exceed the qualifying threshold. In addition, the Applicant provided batch analysis of the drug product that indicated 100% enantiomeric purity. The Applicant did not provide a specification for d-ephedrine sulfate in the drug product. However, the Applicant provided testing for d-ephedrine sulfate at 18 months and none was detected. As such, it appears the degradant is adequately controlled at the level of drug substance.

Osmolality
To date, we have been unable to identify any specific regulations for acceptable osmolarity/osmolality of intravenous drug products which could be used to justify the

safety of an intravenous solutions without the need for dedicated local tissue toxicity studies and blood compatibility studies. This is likely because the risk of thrombophlebitis is multifaceted and each product should be considered on its own; however, osmolarity/osmolality is an important factor for consideration. It is noted that osmolarity refers to the number of solute particles per 1 L of solvent whereas osmolality refers to the number of solute particles in 1 kg of solvent. For dilute aqueous solutions, the difference between osmolarity and osmolality is considered insignificant. According to Stranz and Kastango (2002), the Infusion Nursing Society notes that solutions have an osmolarity of < 500 mOsm/L and a pH of 5-9 to minimize or prevent vascular damage in low flow vessels from extremes of infusate pH or osmolarity, suggesting standard practice and previous human experience with solutions that are hypertonic (Stranz 2002). Other recommendations have noted that parenteral nutrition admixtures of up to 900 mOsm/L are routinely infused peripherally; however, the evidence for the safety is considered weak (Boullata 2014). Boullata et al. appropriately note that the osmolarity of a solution is one contributing factor that can influence the risk of thrombophlebitis. When water moves from the local cells to the blood stream, the cells donating the water shrink. When they shrink at the injection site, the basement membrane of the vein epithelial cell lining is exposed and increases the risk for phlebitis (Rosenthal 2006). Infusion of hypertonic solutions creates an osmotic gradient that draws water out of the cells and increase extracellular volume. For example, 3% NaCl (1030 mOsm/L) is used to treat severe, critical hyponatremia and dextrose solutions (406 mOsmol/L) are used to treat hypovolemia. In these cases, monitoring for fluid overload is an important part of the treatment (Lippincott Nursing Center 2019). The nonclinical data reported by Kuwahara suggest that infusion of hypertonic solutions at a faster rate minimizes the potential for local tissue damage (Kuwahara 1998). According to the Applicant, the referenced product Akovaz, once diluted in physiological saline to 5 mg/mL, ranges from 285 to 304. In contrast, the revised proposed product specification is for Nevakar's product is (b) (4) mOsm/kg. Collectively, the small difference in osmolality of the Nevakar product is not likely to have clinical significance given the small magnitude of the difference, the osmolality is within that of other intravenous solutions administered in clinical practice, the bolus dosing employed, the size of the vessel the drug is usually administered into. This is supported by the referenced published clinical studies and the recommendations of the Infusion Nursing Society intended to minimize local tissue damage. The reader is also referred to the clinical review for additional discussion of this topic given the multidisciplinary manner in which it is being addressed.

Taken together, from a nonclinical pharmacology toxicology perspective, this application may be approved with the recommended labeling changes such that the nonclinical sections of the approved label are identical to the most recent referenced product labeling.

12 Appendix/Attachments

References

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/s/

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I concur.