CENTER FOR DRUG EVALUATION AND RESEARCH

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:	213407
Supporting document/s:	1, 2, 8, 10
CDER stamp date:	June 3, 2019, June 12, 2019, September 26, 2019, October 7, 2019
Product:	Ephedrine sulfate injection
Indication:	Clinically important hypertension in the setting of anesthesia
Applicant:	Nexus Pharmaceuticals
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
Division Director:	Rigoberto Roca, MD (Acting)
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1 Executive Summary

1.1 Introduction

The Applicant is submitting NDA 213407 via the 505(b)(2) regulatory pathway with Akovaz (NDA 208289) as the refenced product. 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 referenced product.

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 contains sodium chloride which is not contained in the referenced product. In the initial NDA submission, the drug product specifications for osmolality differed in comparison to the referenced product for which blood compatibility and local irritation studies would be required. However, the Applicant addressed (b) (4) the osmolality specifications.

The Applicant initially proposed drug substance and drug product impurity specifications for the isomer (+) ephedrine sulfate above the qualifying threshold but has agreed to modify the specifications to NMT (b) (4) % in the drug substance and NMT (b) (4) % in the drug product, which are below the qualification thresholds per ICH Q3A(R2) and Q3B(R2), respectively. The drug product container closure system is a glass vial and stopper. Initially only leachable data from 12 months was included in the NDA submission but the Sponsor provided leachables data from 18 and 24 months in a response to CMC IR. It was also noted early in the review cycle that the extractable studies included only placebo conditions. However, in response to CMC information requests the Applicant submitted additional extractable studies with bracketing pH conditions and also with a harsher solvent, namely 50:50 isopropanol: water. The leachable study identified one impurity that was determined to be a drug product-related impurity that was below the recommended qualification threshold. As such, from a nonclinical pharmacology toxicology perspective, the drug product under review has no differences of concern in comparison to the approved reference product.

1.3 Recommendations

1.3.1 Approvability

From a pharmacology toxicology perspective, NDA 213407 may be approved.

1.3.2 Additional Non Clinical 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 (b) (4)	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.	See the clinical review and/or the MHT review for human data labeling recommendations. These data reflect the most recently approved labeling from the referenced product.
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	Juvenile animal data was recently added to the referenced drug labeling and therefore

	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). **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).	has been added to this label.
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 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** 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.	**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 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** 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.	No changes necessary. Final labeling is identical to the most recently approved Akovaz labeling.

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. Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration *[see Warnings and Precautions 5.2]*.	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. 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 recommended dose on a mg/m^2 basis, respectively). <u>Mutagenesis:</u> Ephedrine sulfate tested negative in the in vitro bacterial reverse	**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 recommended dose on a mg/m^2 basis, respectively). <u>Mutagenesis:</u> Ephedrine sulfate tested negative in the in vitro bacterial reverse	These data reflect the most recently approved labeling from the referenced product.

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) [redacted]	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) [redacted] 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: 134-72-5

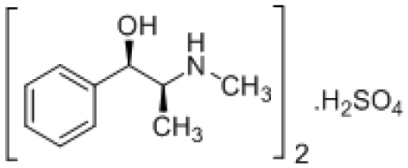
Generic Name: (-) ephedrine sulfate; l-ephedrine; (1R,2S)-(-)-ephedrine

Code Name: n/a

Chemical Name: Benzenemethanol, α-[1-(methylamino) ethyl]-, [R-(R*, S*)]-, Sulfate (2,1)(salt); (1 R, 2 S)-(-)-2-Methylamino-1-phenyl-1-propanol sulfate

Molecular Formula/Molecular Weight: $C_{20}H_{32}N_2O_6S$ /428.54

Structure or Biochemical Description



Pharmacologic Class: alpha- and beta-adrenergic receptor agonist and norepinephrine releasing agent [Established Pharmacological Class]

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) reference product
PIND 128958	Ephedrine sulfate	NEXUS PHARMACEUTICALS INC	DAAP	Presubmission
DMF (b) (4)	Drug Substance	(b) (4)	DRM	Active Referenced by several FDA approved products
DMF	(b) (4)		DRM	Active
DMF			DRM	Active
DMF			DRM	Active

2.3 Drug Formulation

The composition of the Applicant's ephedrine sulfate injection differs from the reference product in that it is designed to not require dilution whereas the reference product is designed to be diluted (b) (4) before use.

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

Per the Applicant's submission:

Ephedrine Sulfate Injection, 5 mg/mL, 50 mg/10 mL vial (EPH-001)			
Component	**Function**	**Unit (mg per mL)**	**Unit (% w/w)**
Ephedrine Sulfate, USP	Active	5	(b) (4)
Sodium Chloride	(b) (4)	9	
Water for Injection, USP		q.s. to 1 mL	

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) at levels greater than those in the proposed ephedrine sulfate drug product when calculated for concentration and maximum daily dose.

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

Ingredients	Function	Amount (mg/mL)	Maxiumum exposure (mg/day)	Acceptable? (Rationale)
Sodium chloride	(b) (4)	9.0	(b) (4)	Yes (IID)
Water for injection		q.s. to 1 mL		Yes (IID)

IID: FDA Inactive Ingredient Database

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

The drug substance impurity specifications are presented in the table below. The identification threshold according to ICH Q3A(R2) for a MDD of ≤ 2g/day is 0.10% or 1.0 mg/day intake, whichever is lower. The qualification threshold according to ICH Q3A(R2) for an MDD of ≤ 2g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant is referencing (b) (4) for ephedrine sulfate drug substance. The drug substance impurity specifications are presented in the table below. The Applicant has set a specification of NMT (b) (4)% for any unspecified individual impurity, which is acceptable. In their initial submission the Applicant proposed a drug substance specification of NMT (b) (4)% for (+) ephedrine sulfate, which exceeded the qualification threshold. Following an information request from CMC the Applicant agreed to modify the specification to NMT (b) (4)%, which does not exceed the qualification threshold.

Table 5. Drug Substance Impurities and Qualification Status

Impurity/ Degradants	Structure	Proposed Specification	Comment

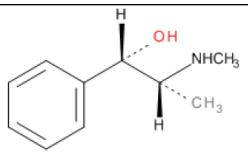
(+) Ephedrine		NMT 0 (b) (4) %	Acceptable. The proposed specification is below the qualifying threshold per Q3A(R2).
(b) (4)			Acceptable. The proposed specification is within the range of the referenced drug product.
			Acceptable. The proposed specification is below the qualifying threshold as described in ICH Q3A (R2).

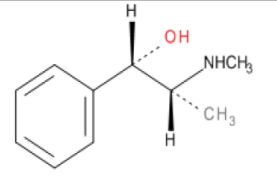
Table 6. Residual Solvents and Qualification Status

Residual Solvent	Specification		Comment
(b) (4)	NMT	(b) (4)	Acceptable, meets ICH Q3C threshold of (b) (4) ppm for a (b) (4) residual solvent
	NMT		Acceptable, meets ICH Q3C threshold of (b) (4) ppm for a (b) (4) residual solvent
	NMT		Acceptable, meets ICH Q3C threshold of (b) (4) ppm for this (b) (4) residual solvent

Drug Product Degradants

In their initial submission the Applicant proposed a drug product specification of NMT (b) (4) % for (+) ephedrine sulfate, which exceeded the qualifying threshold. Following an information request from CMC the Applicant agreed to modify the specification to NMT (b) (4) % which does not exceed the qualifying threshold. The Applicant did not provide specifications for any other impurities or degradants beyond (+) ephedrine sulfate.

Table 7. Drug Products Impurities and Qualification Status

Impurity/ Degradants	Structure	Proposed Specification	Comment
(+) Ephedrine		NMT (b) (4) %	Acceptable. The proposed specification is below the qualifying threshold of 0.5%.
Any unspecified impurity		NMT (b) (4) %	Acceptable. The proposed specification is below the identification threshold.

The Applicant provided stability testing data for 3, 6, 9, 12, and 18 months at ambient temperatures. No degradants were observed.

Table 8. Constituents of the Container Closure System

Per the Applicant's submission:

Container / Closure System		
Item	**Part No.**	**Description**
Container		(b) (4)
Closure		
Seal		

Extractable Studies

The Applicant initially submitted extractable studies for individual manufacturing components tested separately (b) (4) and container closure components (stoppers) using "placebo" conditions with higher than ambient heat (b) (4) but did not evaluate for extractables under more rigorous extraction conditions such as acidic or basic conditions or using organic solvents. In response to CMC information requests the Applicant submitted an extractable/leachable study on February 27, 2020. Extraction solvents included pH 3.4 water, pH 9.4 water, and 50:50 isopropanol:water mixture (the reader is referred to the CMC review for the adequacy of the solvents tested). The Applicant utilized an analytical threshold of (b) (4) ppm) and a qualifying threshold of (b) (4) ppm) in their evaluation, which is acceptable (see calculations below).

Acceptable AET calculation:

Safety Concern Threshold (SCT) = (b) (4)

Maximum daily dose of ephedrine sulfate (MDD) = 50 mg/day

Concentration of drug product = 5 mg/mL

Maximum daily volume (MDV) = 10 mL/day

Analytical Evaluation Threshold (AET) = SCT/MDV = (b) (4)

The SCT is appropriate. The following extractables were found at greater than the AET of (b) (4).

Table 9. Summary of Detected Extractable Compounds and Qualification Status

Extractables	CAS	Maximum daily intake* (mcg/day)			Reasonable? (Rationale)
		pH 3.4 water	pH 9.4 water	50:50 isopropanol: water	
Volatiles and semi-volatiles					

[redacted] (b) (4)	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.
	Not detected above analytical threshold in leachable study.

Leachable Studies

The Applicant submitted leachable study data from three batches of drug product stored for 12 months, 18 months, and 24 months at 25°C ± 2°C and 60% ± 5% relative humidity in the upright and inverted orientation with drug product in contact with the rubber stopper. The same three batches were evaluated at each timepoint. The Applicant utilized an AET of of [redacted] (b) (4) ppm) for LC-MS and [redacted] (b) (4) ppm) for GC-MS. The reader is referred to the CMC review for the adequacy of the leachables methodology and data. As per the CMC review team, the data adequately predict the trends for potential leachable over the course of the proposed shelf life and characterize the likely highest level present in the drug product. The lack of data from early timepoints has been discussed with the CMC review team. The CMC team has concluded that in this case, in part based on the use of this stopper in other FDA-approved drug products and analysis of the existing data, the data are adequate to inform the toxicological risk assessment.

Table 10. Leachable Study Conditions

Timepoint	Conditions	Analysis	Batch Lots

12 months	25°C ± 2°C and 60% ± 5% relative humidity	GCMS QTOF LC-MS QTOF HPLC	V017A17A V018A17A V019A17A
18 months	25°C ± 2°C and 60% ± 5% relative humidity	GCMS QTOF LC-MS QTOF HPLC	V017A17A V018A17A V019A17A
24 months	25°C ± 2°C and 60% ± 5% relative humidity	GCMS QTOF LC-MS QTOF HPLC	V017A17A V018A17A V019A17A

There were no leachable compounds that were reported to be higher than the AET with the exception of (b) (4) which was observed in multiple samples at a highest level of (b) (4) (maximum daily dose would be (b) (4) with a maximum volume of 10 mL to deliver the MDD of 50 mg/day). The Applicant did not submit a QSAR evaluation of this compound to determine if the copound contains a structural alert for mutagenicity. However, from a genetic toxicology perspective, these levels would be acceptable for this acute-use product even if the compound were DNA reactive. (b) (4) In support of this supposition, (b) (4) was not detected in any of the placebo extracts, which are samples that do not contain the API. CMC agrees that (b) (4) is a drug product impurity that should be limited by ICH Q3B(R2). The highest reported levels of (b) (4) ppm corresponding to (b) (4) % is well below the qualifying thresholds for drug product impurities based on the MRHD of 50 mg and therefore is acceptable.

Elemental Impurities

The Applicant examined the final drug product for elemental impurities in accordance with ICH Q3D. The Applicant elected to evaluate each component of the drug product separately and the manufacturing process for potential elemental impurities (Option 1) and evaluated the final drug product for elemental impurities as well. Three inverted lots were examined including a long-term stability sample. The Applicant reports that there are no elemental impurities present in the drug product above permissible daily exposure limits listed in ICH Q3D. See CMC review for evaluation of the methodology employed.

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant is pursuing 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

(b) (4)

2.7 Regulatory Background

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

The Applicant submitted a PIND meeting package on September 26, 2016 under IND 128958. Written responses were conveyed to the Applicant on November 21, 2016. Excerpts of the nonclinical comments that were communicated to the Applicant are shown below:

Question 4:
Does the Division agree that Nexus' proposal to summarize literature will likely satisfy the toxicology portion of the application?

FDA Response to Question 4:

For a 505(b)(2) application to support a general indication of "treatment of clinically important hypotension in the setting of anesthesia" that relies entirely upon information in the public domain, nonclinical literature alone is not adequate to support an NDA application. The existing data do not appear to contain adequate information regarding the in vivo mutagenic potential and impact on reproductive and developmental toxicity of ephedrine. You may consider relying on the Agency's previous finding of safety as it is reflected in the approved labeling for an approved listed drug. Otherwise these nonclinical studies may be necessary as postmarketing requirements (PMRs). If you are not planning on to rely on the Agency's previous finding of safety of a listed drug, prior to the reproductive and developmental toxicology studies being submitted, the drug product will likely be labeled with a risk statement equivalent to a Pregnancy Category C due to lack of adequate nonclinical data. In the absence of adequate clinical data for these endpoints, the lack of these nonclinical studies will likely impact your final drug product labeling with respect to use during C-sections. Final determination regarding whether PMRs will be required can only be provided upon detailed review of the referenced literature studies. Note that any reference to published literature should specifically indicate what stereoisomers were tested and provide justification for why those data are relevant to your drug product.

As your product will be administered via the intravenous (IV) route of administration, your NDA submission must provide data to demonstrate blood compatibility and lack of adverse local tissue irritation. This may be addressed via tonicity data and clinical use data in the published literature if you can provide data to show that the formulations tested in the literature are comparable to your proposed formulation and the lack of any apparent novel excipients via the IV route of administration in your proposed formulation. However, final determination of the adequacy of the submitted materials can only be provided at the time of NDA review.

Additional boilerplate language regarding general nonclinical recommendations was also communicated to the Applicant with regards to novel excipients, impurities, extractables/leachables, and labeling.

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 study 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

There were no special toxicology studies with ephedrine sulfate submitted in this NDA. Initially, the drug product specifications differed in osmolality compared to the reference product. This would have required blood compatibility (hemolysis, flocculation of proteins, platelet activation) and local irritation studies to be conducted to support safety of a change in formulation. However, the Applicant modified the osmolality specification for the drug product to be comparable to the referenced product and therefore no additional studies were required.

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

There were no new toxicology studies submitted or required to support this NDA as the drug product (b) (4) to the referenced product with the exception that this drug product does not require dilution prior to administration. The Applicant initially proposed drug substance and drug product impurity specifications for the isomer (+) ephedrine sulfate that was above the respective qualifying thresholds but has agreed to modify the specifications to be within qualification thresholds stated in Q3A(R2) and Q3B(R2).

In the initial NDA submission the Applicant only submitted extractable studies under placebo conditions that were considered inadequate to assess safety. However, in response to CMC information requests, the Applicant submitted extractions studies using pH 3.4, pH 9.4, and 50:50 isopropanol:water. The Applicant also submitted leachable study data at 18 and 24 months. None of the identified extractables above the analytical threshold were detected above the recommended 5 mcg/day safety concern threshold in the leachable studies. CMC indicates the studies are acceptable. The Applicant identified another impurity, (b) (4) used in the manufacturing process of the drug substance. However, levels in the leachable studies did not rise above the relevant qualifying threshold (200 mcg/mL).

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 is identical to the most recent referenced product labeling.

12 Appendix/Attachments

Literature Cited:

Plosnik A, Vracko M and Dolenc MS (2016) Mutagenic and carcinogenic structural alerts and their mechanisms of action. *Arh Hig Rada Toksikol* **67**:169-182.

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/s/

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04/14/2020 03:34:28 PM

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I concur.