CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208289Orig1s006

Trade Name:	Akovaz®
Generic or Proper Name:	ephedrine sulfate injection for intravenous use
Sponsor:	Exela Pharma Sciences, LLC
Approval Date:	08/02/2021
Indication:	AKOVAZ® injection is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

APPROVAL LETTER

NDA 208289/S-006

SUPPLEMENT APPROVAL

Exela Pharma Sciences, LLC
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Attention: Aruna Koganti
Vice President Regulatory Affairs and Clinical Programs

Dear Ms. Koganti:

Please refer to your supplemental new drug application (sNDA) dated and received November 10, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Akovaz (ephedrine sulfate injection, USP).

This Prior Approval supplemental new drug application provides for the addition of a new presentation of ready-to-use Akovaz 25 mg/5 mL (5 mg/mL) prefilled in a 5 mL (b) (4) syringe, as well as changes to the labeling to reflect this new presentation.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

As originally raised in our March 3, 2021, email communication, we encourage you to continue to discuss with the Drug Enforcement Agency (DEA) the impact of release and stability specifications for the (b) (4) impurity, a schedule I controlled substance, in your product. We understand from your June 4, 2021, submission that, at the advice of the DEA, you have submitted to DEA a request for exemption under 21 U.S.C. 811(g)(3)(A) and 21 CFR 1307.03.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry, *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry, *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labeling for approved NDA 208289/ S-006**." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information aabout submitting promotional materials, see the final guidance for industry, *Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertisign in Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

[21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Kimberly Compton, RPh, RAC, Sr. Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

RIGOBERTO A ROCA
08/02/2021 01:11:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AKOVAZ® safely and effectively. See full prescribing information for AKOVAZ.

AKOVAZ (ephedrine sulfate injection) for intravenous use
Initial U.S. Approval: 2016

---------- INDICATIONS AND USAGE ----------
AKOVAZ injection is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Should be administered by trained healthcare providers (2.1)
- AKOVAZ injection, 50 mg/mL, must be diluted before administration as an intravenous bolus dose. (2.1)
- AKOVAZ injection, 5 mg/mL in a pre-filled syringe, is a premixed formulation. Do not dilute prior to use. (2.1)
- Bolus intravenous injection: 5 mg to 10 mg as needed, not to exceed 50 mg. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 50 mg/mL ephedrine sulfate in single-dose vial and 25 mg/5 mL (5 mg/mL) ephedrine sulfate in a 5 mL single-dose prefilled syringe (3)

---------- CONTRAINDICATIONS ----------
None (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pressor Effects with Concomitant Use with Oxytocic Drugs: Pressor effect of sympathomimetic pressor amines is potentiated (5.1)
- Tachyphylaxis and Tolerance: Repeated administration of ephedrine may cause tachyphylaxis (5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions during treatment: nausea, vomiting, and tachycardia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Exela Pharma Sciences, LLC at 1-888-451-4321 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------
- Interactions that Augment Pressor Effect: clonidine, oxytocin and oxytocic drugs, propofol, monoamine oxidase inhibitors (MAOIs), and atropine. Monitor blood pressure. (7)
- Interactions that Antagonize the Pressor Effect: Antagonistic effects with α-adrenergic antagonists, β-adrenergic antagonists, reserpine, quinidine, mephentermine. Monitor blood pressure. (7)
- Guanethidine: Ephedrine may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness. Monitor blood pressure and adjust the dosage of pressor accordingly.
- Rocuronium: Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction. Be aware of this potential interaction. No treatment or other interventions are needed.
- Epidural anesthesia: Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia. Monitor and treat the patient according to clinical practice.
- Theophylline: Concomitant use of ephedrine may increase the frequency of nausea, nervousness, and insomnia. Monitor patient for worsening symptoms and manage symptoms according to clinical practice.
- Cardiac glycosides: Giving ephedrine with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias. Carefully monitor patients on cardiac glycosides who are also administered ephedrine.

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AKOVAZ (ephedrine sulfate injection) is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration Instructions

AKOVAZ (ephedrine sulfate injection), 50 mg/mL must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.

AKOVAZ (ephedrine sulfate injection), 25 mg/5 mL (5 mg/mL) in a prefilled syringe, is a premixed formulation. Do not dilute prior to use. The single-dose prefilled syringe is intended for use in one patient during one surgical procedure. Discard any unused portion.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Dosing for the Treatment of Clinically Important Hypotension in the Setting of Anesthesia

AKOVAZ should be administered by trained healthcare providers.

The recommended dosages for the treatment of clinically important hypotension in the setting of anesthesia is an initial dose of 5 mg to 10 mg administered by intravenous bolus. Administer additional boluses as needed, not to exceed a total dosage of 50 mg.

- Adjust dosage according to the blood pressure goal (i.e., titrate to effect).

2.3 Prepare a 5 mg/mL Solution for Bolus Intravenous Administration

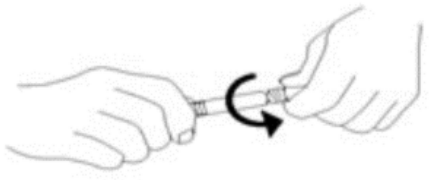
For bolus intravenous administration, prepare a solution containing a final concentration of 5 mg/mL of AKOVAZ (ephedrine sulfate injection):

- Withdraw 50 mg (1 mL of 50 mg/mL) of AKOVAZ (ephedrine sulfate injection) and dilute with 9 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
- Withdraw an appropriate dose of the 5 mg/mL solution prior to bolus intravenous administration.

2.4 Instructions for Use of Prefilled Syringe

1. Perform visual inspection on the syringe by verifying:
   - Absence of syringe damage
   - Absence of external particles
   - Absence of internal particles
   - Proper drug color
   - Drug name
   - Drug strength
   - Fill volume
   - Route of administration
   - Expiration date to be sure the drug has not expired
2. Do not remove the tamper evident seal. Push plunger rod slightly in to break the stopper loose while tip cap is still on.
3. Remove tip cap and tamper evident seal by twisting off. (See Figure 1):

   Figure 1.



4. Discard the tip cap.
5. Expel air bubble.
6. Adjust dose into sterile material (if applicable).
7. Connect the syringe to an appropriate intravenous connection.
   - Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).
8. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.
9. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle.
   - To prevent needle stick injuries, do not recap needle when needle is connected to syringe.

NOTE: All steps must be done sequentially

- Do not re-sterilize syringe
- Do not use this product on a sterile field
- Do not introduce any other fluid into the syringe at any time
- This product is for single dose only

3 DOSAGE FORMS AND STRENGTHS

AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection available as :

single-dose 1 mL vial that contains 50 mg/mL ephedrine sulfate, equivalent to 38 mg/mL of ephedrine base

single-dose 5 mL prefilled syringe that contains 25 mg/ 5 mL (5 mg/mL) ephedrine sulfate equivalent to 19 mg/5 mL (3.8 mg/mL) of ephedrine base

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pressor Effect with Concomitant Oxytocic Drugs

Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine) [*see Drug Interactions (7)*]. Some of these patients experienced a stroke. Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.

5.2 Tolerance and Tachyphylaxis

Data indicate that repeated administration of ephedrine can result in tachyphylaxis. Clinicians treating anesthesia-induced hypotension with AKOVAZ (ephedrine sulfate injection) should be aware of the possibility of tachyphylaxis and should be prepared with an alternative pressor to mitigate unacceptable responsiveness.

5.3 Risk of Hypertension When Used Prophylactically

When used to prevent hypotension, ephedrine has been associated with an increased incidence of hypertension compared with when ephedrine is used to treat hypotension.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of ephedrine sulfate were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Gastrointestinal disorders: Nausea, vomiting

Cardiac disorders: Tachycardia, palpitations (thumping heart), reactive hypertension, bradycardia, ventricular ectopics, R-R variability

Nervous system disorders: Dizziness

Psychiatric disorders: Restlessness

7 DRUG INTERACTIONS

Interactions that Augment the Pressor Effect	
Oxytocin and oxytocic drugs	
Clinical Impact:	Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine). Some of these patients experienced a stroke.
Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.
Clonidine, propofol, monoamine oxidase inhibitors (MAOIs), atropine	
Clinical Impact:	These drugs augment the pressor effect of ephedrine.
Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs.
Interactions that Antagonize the Pressor Effect	
Clinical Impact:	These drugs antagonize the pressor effect of ephedrine.
Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs.
Examples:	α-adrenergic antagonists, β-adrenergic receptor antagonists, reserpine, quinidine, mephentermine
Other Drug Interactions	
Guanethidine	
Clinical Impact:	Ephedrine may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness.
Intervention:	Clinician should monitor patient for blood pressor response and adjust the dosage or choice of pressor accordingly.
Rocuronium	
Clinical Impact:	Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction.
Intervention:	Be aware of this potential interaction. No treatment or other interventions are needed.
Epidural anesthesia	

Clinical Impact:	Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia.
Intervention:	Monitor and treat the patient according to clinical practice.
Theophylline	
Clinical Impact:	Concomitant use of ephedrine may increase the frequency of nausea, nervousness, and insomnia.
Intervention:	Monitor patient for worsening symptoms and manage symptoms according to clinical practice.
Cardiac glycosides	
Clinical Impact:	Giving ephedrine with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias.
Intervention:	Carefully monitor patients on cardiac glycosides who are also administered ephedrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 due to underlying conditions *(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 are 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 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Untreated hypotension associated with spinal anesthesia for cesarean section is associated with an increase in maternal nausea and vomiting. A decrease in uterine blood flow due to maternal hypotension may result in fetal bradycardia and acidosis.

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).

8.2 Lactation

Risk Summary

A single published case report indicates that ephedrine is present in human milk. However, no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AKOVAZ (ephedrine sulfate injection) and any potential adverse effects on the breastfed child from AKOVAZ (ephedrine sulfate injection) or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of AKOVAZ 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).

8.5 Geriatric Use

Clinical studies of ephedrine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

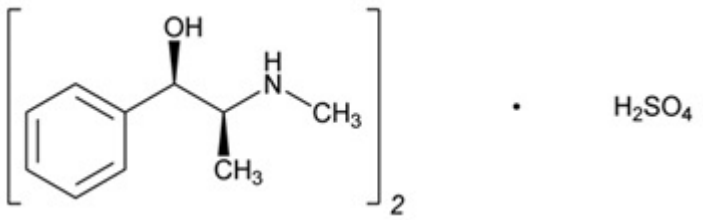
Ephedrine and its metabolite are excreted in urine. In patients with renal impairment, excretion of ephedrine is likely to be affected with a corresponding increase in elimination half-life, which will lead to slow elimination of ephedrine and consequently prolonged pharmacological effect and potentially adverse reactions. Monitor patients with renal impairment carefully after the initial bolus dose for adverse events.

10 OVERDOSAGE

Overdose of ephedrine can cause a rapid rise in blood pressure. In the case of an overdose, careful monitoring of blood pressure is recommended. If blood pressure continues to rise to an unacceptable level, parenteral antihypertensive agents can be administered at the discretion of the clinician.

11 DESCRIPTION

Ephedrine is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection. The chemical name of ephedrine sulfate is benzenemethanol, α-[1-(methylamino)ethyl]-, [*R*-(*R**,*S**)]-, sulfate (2:1) (salt), and the molecular weight is 428.5 g/mol. Its structural formula is depicted below:



Ephedrine sulfate is freely soluble in water and ethanol, very slightly soluble in chloroform, and practically insoluble in ether.

Each mL of the 50 mg/mL strength contains ephedrine sulfate 50 mg (equivalent to 38 mg ephedrine base) in water for injection. The pH is adjusted with sodium hydroxide and/or glacial acetic acid if necessary. The pH range is 4.5 to 7.0. The 50 mg/mL vial must be diluted before intravenous administration.

Each mL of the 5 mL single-dose prefilled syringe contains 5 mg ephedrine sulfate (equivalent to 3.8 mg ephedrine base) and 9 mg Sodium Chloride, USP in Water for Injection. The pH range is 4.5 to 6.5.

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. 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)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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).

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: 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.

14 CLINICAL STUDIES

The evidence for the efficacy of ephedrine injection is derived from the published literature. Increases in blood pressure following administration of ephedrine were observed in 14 studies, including 9 where ephedrine was used in pregnant women undergoing neuraxial anesthesia during Cesarean delivery, 1 study in non-obstetric surgery under neuraxial anesthesia, and 4 studies in patients undergoing surgery under general anesthesia. Ephedrine has been shown to raise systolic and mean blood pressure when administered as a bolus dose following the development of hypotension during anesthesia.

16 HOW SUPPLIED/STORAGE AND HANDLING

AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection supplied as follows:

NDC	Strength	How Supplied
51754-4200-4	50 mg/mL of ephedrine sulfate equivalent to 38 mg/mL of ephedrine base	1 mL clear glass vial; for single-dose (supplied in packages of 25)
51754-4250-3	25 mg/ 5 mL (5 mg/mL) of ephedrine sulfate equivalent to 19 mg/5 mL (3.8 mg/mL) of ephedrine base	5 mL single-dose prefilled syringe (supplied in packages of 10)

Vial stoppers are not manufactured with natural rubber latex. Store AKOVAZ (ephedrine sulfate injection), at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in carton until time of use. For single dose only. Discard unused portion.

The single-dose 5 mL prefilled syringe is intended for use in one patient during one surgical procedure.

Manufactured for:

Exela Pharma Sciences, LLC

Lenoir, NC 28645

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

SUMMARY REVIEW

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

COMBINED PHARMACOLOGY/TOXICOLOGY AND DIVISION DIRECTOR NDA SUPPLEMENT REVIEW AND EVALUATION

Application number:	NDA 208289/S-006
Supporting document/s:	84, 85, 86, 90, 91, 93, 94
CDER stamp date:	November 10, 2020; January 15, 2021; January 21, 2021; March 5, 2021; March 11, 2021, March 28, 2021; June 4, 2021
Product:	Akovaz (ephedrine sulfate)
Indication:	Treatment of (b) (4)
Applicant:	Exela Pharma Sciences LLC
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Casandra Cartagena, MS, PhD
Supervisor/Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Kimberly Compton, RPh, RAC

Template Version: September 1, 2010

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208289 are owned by Exela Pharma Sciences or are data for which Exela Pharma Sciences has obtained a written right of reference. Any information or data necessary for approval of NDA 208289 that Exela Pharma Sciences does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208289.

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Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant has submitted a prior approval supplement seeking marketing approval for a 5 mg/mL ephedrine sulfate in a 5 mL syringe (25 mg/syringe) to be used as an injectable intravenous solution for the treatment of clinically important hypotension. This drug product does not require dilution before use. The original NDA for 50 mg/mL ephedrine sulfate, which requires dilution before use, was approved April 29, 2016.

NONCLINICAL REVIEW

1.2 Brief Discussion of Nonclinical Findings

Given that the new presentation is a ready to use prediluted formulation, any differences in physicochemical properties when compared to the initially approved concentrated formulation in a vial presentation would have to be justified for safety. In the initial submission, the Applicant (b) (4) the original approved concentrated product has an osmolality range of 280-320 mOsm/kg. During the review process the Division (b) (4). In response, the Applicant (b) (4) (b) (4) The is within whole blood osmolality levels and other commonly used IV solutions (See discussion below), the dosing regimen is an acute bolus dose, and the administration of ephedrine will likely be diluted given the dead space between the injection port and the catheter injection site; Therefore, the (b) (4) drug product and the reference product is unlikely to raise any safety concerns.

There are no safety concerns with the drug product formulation as there are no novel excipients. Specifications for drug substance and drug product impurities are acceptable as all the impurities do not exceed ICH Q3A and Q3B qualification thresholds. However, there was one unique drug product degradant that is not detected in the currently approved, more concentrated drug product, known as (b) (4), which is a Schedule I substance. The Applicant has set a specification of NMT than (b) (4) for this drug product degradant. From a nonclinical toxicology perspective, the specification is acceptable because the proposed specification is below the qualification threshold as described in ICH Q3B(R2) and that the maximum daily intake of 50 mcg/day does not raise any toxicological safety concerns. We defer to the Controlled Substance Staff (CSS) regarding the acceptability and implications of the presence of this degradant in the drug product.

To support the safety of the new container closure system, the Applicant submitted an extractables/leachables assessment of the syringe. In the Applicant's leachable studies (b) (4) were detected at greater than the qualifying threshold of 5 mcg/day ((b) (4) However, (b) (4) levels were within the (b) (4)

(b) (4) calculated by this Reviewer. Although several compounds had LOQs that were above the qualification threshold, the LOD was able to detect the compound (b) (4) with the exception of one compound which was (b) (4). The LOQ and LOD was (b) (4) and taking into consideration the maximum daily dose of ephedrine, the maximum intake of (b) (4). (b) (4) is generally recognized as safe (GRAS) and is present in foods and is also used as an additive. The maximum daily intake of (b) (4) via the diet can be up to (b) (4) for a 60 kg human. Studies have demonstrated that this compound is highly bioavailable and therefore, the maximum daily intake of (b) (4) via use with this drug product is significantly lower that then levels in achieved from the diet. It is also noted that this syringe is used in several FDA approved intravenous products with comparable physicochemical properties. Taken together, there are no safety concerns regarding leachables in the drug product.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 208289 prior approval supplement for the 5 mL syringe presentation may be approved.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The nonclinical sections of the final drug product labeling are identical to the most recently approved Akovaz drug product labeling and therefore there are no labeling edits recommended at this time.

1.3.4 Division Director's Statement and Recommendation for Action

Drs Rohit Kolhatkar, Gurpreet Gill Sangha, Laura Wasil, Swapna Pamu, Vani Richards completed the Product Quality (CMC) review, which summarizes the conclusions of the CMC team (including facilities, microbiology, and biopharmaceutics). The CMC review team has concluded that adequate information on the physicochemical properties of the proposed prefilled syringe, in-process controls in the manufacturing process to ensure quality assurance, adequate sterility assurance, and adequate stability data to support the proposed shelf-life of 24 months. It is noted that the Applicant added limits for (b) (4) for the proposed new 5-mL prefilled syringe. This (b) (4) compound and is not currently controlled in the vial configuration. The proposed limit for (b) (4) as per the amendment dated 3/5/2021 is NMT (b) (4) stability and below QL at the release. The proposed limit is acceptable from the drug product quality standpoint as per ICH guidelines. The biopharmaceutics team of Drs. Swapna Pamu and Hansong Chen concluded that a biowaiver request can be granted.

The CMC team concluded that the PAS can be approved in its present form, with the comment that the drug product specifications list [redacted], which is a [redacted] substance. The CMC review teams defers to the Controlled Drug Substance Staff and DEA for the acceptability of the presence of the [redacted] substance in the drug product. The CMC team also noted that [redacted] is also referred to as [redacted] and is a known degradant present in multiple FDA-approved [redacted] containing drug products.

Drs. Casandra Cartagena, Newton Woo, and Dan Mellon completed the nonclinical pharmacology toxicology review. As per their review below, the review team concluded that there are no safety concerns with the osmolality range of [redacted] mOsm/kg of the prediluted ready to use formulation and with the identification of the [redacted], which is a Schedule I substance. This specification is below ICH [redacted] qualification thresholds and the maximum daily intake of [redacted] for this Schedule 1 substance does not raise any toxicological safety concerns. The review team also concluded that the Applicant provided adequate extractable leachable data to support the safety of the new container closure system, consisting of a [redacted]. Therefore, the nonclinical review team recommends approval of Supplement 6.

Drs. Cameron Johnson and Ebony Whaley completed the labeling review for the Division of Medication Error Prevention and Analysis (DMEPA). They have concluded that the revised carton labeling is acceptable.

Regarding the [redacted] the Agency (including the Controlled Substances Staff) discussed the implications of this impurity with the Applicant and recommended that the Applicant contact DEA to determine if the drug product requires scheduling or if an exemption from scheduling could be granted by DEA for this drug product. The Applicant submitted documentation on June 4, 2021 that they contacted the DEA to discuss this issue. As per Exela, DEA indicated that "Exela submit an exemption request [redacted] A copy of the exemption request submitted to DEA by Exela as also included in that submission. The DEA has not yet responded to this request.

Through the Controlled Substances Staff (CSS), DAAP was informed by the Office of the Chief Counsel (Sherene Sepehri, email dated 5/20/2021) that DAAP can approve the drug product under the FD&C Act and that the control issues would fall under DEA's purview.

I (Rigoberto Roca) have reviewed the CMC review, the nonclinical pharmacology toxicology review (below), and the DMEPA review and concur with the conclusions of the review teams. The submission adequately addresses the safety of the new ready to infuse syringe presentation. Therefore, Supplement 6 can be approved.

2 Drug Information

2.1 Drug

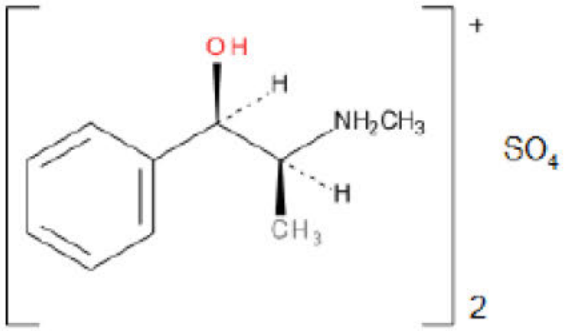
CAS Registry Number: 134-72-5

Generic Name: Ephedrine Sulfate

Code Name: Akovaz

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 g/mol

Structure or Biochemical Description:



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

2.2 Relevant NDAs and DMFs

DMF Number	Subject	Holder	DMF Type	Status
(b) (4)	Drug Substance	(b) (4)		Active
(b) (4)	Syringes	(b) (4)	III	Active

NDA Number	Applicant	Product	Indication	Status (Date)
208-289	Exela Pharma Sciences, formerly Avadel Legacy Pharmaceuticals LLC	Akovaz (Ephedrine Sulfate) injection	Treatment of clinically important hypotension in the setting of anesthesia	Approved, April 29, 2016

2.3 Drug Formulation

The original formulation contained ephedrine sulfate in water for injection (50 mg/mL) that must be diluted in normal saline or 5% dextrose in water. The new presentation is a preservative free, isotonic solution that is ready to use for intravenous administration. The concentration for this formulation is 5 mg/mL and does not have to be diluted prior to intravenous use, whereas the previously approved concentrated 50 mg/mL formulation must be diluted with normal saline or 5% dextrose in water prior to use.

Table 1: Drug Product Unit Composition

Component	Quality Standard	Function	Amount per unit basis (per 5 mL syringe)
Ephedrine Sulfate	USP	Drug substance	25 mg
Sodium Chloride	USP	Tonicity Agent	45 mg
Water for Injection	USP	Solvent	(b) (4)

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 2. Excipients Included in the Drug Product and Qualification Status

Ingredients	Function	Amount (mg/mL)	Maximum exposure (mg/day)	Acceptable? (Rationale)
Sodium Chloride	Tonicity Agent	9	90	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 an 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 DMF (b) (4) for the 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. The identified impurities have a specification NMT (b) (4) or lower, which does not exceed the qualification threshold.

Table 3. Drug Substance Impurity Specifications and Qualification Status

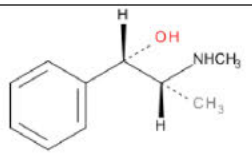
Impurity/ Degradants	Structure	Proposed Specification	Comment
(+) Ephedrine		NMT (b) (4)	Acceptable. The proposed specification is below the qualification threshold per Q3A(R2).
(b) (4)	(b) (4)	NMT (b) (4)	Acceptable. The proposed specification is below the qualification threshold as described in ICH Q3A(R2).
Any unknown impurity		NMT (b) (4)	Acceptable. The proposed specification is below the qualification threshold as described in ICH Q3A(R2).

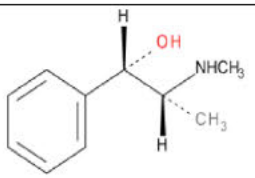
Table 4. Residual Solvents and Qualification Status

Residual Solvent	Specification	Comment
(b) (4)	NMT (b) (4)	Acceptable, meets (b) (4) threshold of (b) (4) ppm for a Class 3 residual solvent
(b) (4)	NMT (b) (4)	Acceptable, meets (b) (4) threshold of (b) (4) ppm for a Class 3 residual solvent
(b) (4)	NMT (b) (4)	Acceptable, meets (b) (4) threshold of (b) (4) ppm for this Class 2 residual solvent

Drug Product

Table 5: Drug Product Degradant Specifications and Qualification Status

Test	Structure	Proposed Specification (NMT)	Comment

(+) Ephedrine		NMT (b) (4)	Acceptable. The proposed specification is below the qualification threshold as described in ICH Q3B(R2).
(b) (4)	(b) (4)	NMT (b) (4)	(b) (4) is not detected in the currently approved, more concentrated drug product. From a toxicology perspective, the specification is acceptable because the proposed specification is below the qualification threshold as described in ICH Q3B(R2). However, it is noted that methcathione is a controlled substance that is classified as Schedule I. It is noted by the Applicant that that (b) (4) may be formed by the oxidation of ephedrine in this more dilute presentation. At the MDD (50 mg/day) the (b) (4) specification of 0.1% equates to a possible exposure of 50 mcg/day. In DP batch analysis (b) (4) was not detected above 0.1% We defer to the Controlled Substance Staff (CSS) regarding the acceptability and implications of the presence of this degradant in the drug product.
Pseudoephedrine		NMT (b) (4)	Acceptable. The proposed specification is below the qualifying threshold as described in ICH Q3B(R2).
Unspecified Impurity		NMT (b) (4)	Acceptable. The proposed specification is below the identification threshold as described in ICH Q3B(R2).
Osmolality		(b) (4) mOsm/kg	Acceptable. The osmolality does not raise safety concerns. See discussion below.
pH		4.5 (b) (4)	Within approved labeled range of 4.5 to 7.0 for the concentrated 50 mg/mL product.

The Applicant [redacted] the original approved product in NDA 208289 has an osmolality of 280-320 mOsm/kg (prior to dilution). During the review process the Applicant was asked [redacted] The Applicant [redacted] given that their current processes [redacted] the original approved drug of 280 to 320 mOsm/kg. From a nonclinical perspective this small adjustment for the [redacted] was considered acceptable (see Section 10 Local Tolerance).

Container Closure System

Ephedrine sulfate injection will be filled in 5 mL [redacted] with a plastic tip cap using a [redacted] (see Table below).

Component	Manufacturer	Supplier	DMF
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

It is noted that there are several approved products marketed using the proposed container closure system.

Extractable Studies

The Applicant conducted extraction studies with the individual components that were further broken down into pieces to expose more surface area to the extraction solvent. Several extraction conditions and solvents were utilized that included [redacted] with water at various pH (i.e., pH [redacted], and [redacted], [redacted] with [redacted]), and [redacted].

The Applicant utilized an analytical threshold of 0.15 mcg/mL ([redacted] and a qualifying threshold of [redacted] (5 mcg/day, [redacted]) in their evaluation, which is acceptable (see Applicant's calculations below).

Table 1. Formulas and Calculations for the SCT and AET Values for Ephedrine Sulfate Injection							
Max Daily Dose Ephedrine Sulfate =	(b) (4)	µg/day					
[Ephedrine Sulfate]-DP =		µg/mL					
Max Daily Dose Volume =		mL/day					
Safety Concern Threshold (SCT) =	(b) (4)	µg/day	Qualification Threshold (QT)	(b) (4)	µg/day	(b) (4)	µg/day
Analytical Evaluation Threshold (AET) =		ppb	Analytical Evaluation Threshold (AET)		ppb		ppb

Note: ppb for the AET are expressed in units of w/v with respect to maximum daily dose volume of the drug product.
* - Refers to the ICH M7 (ref. 15) limit for acceptable intake of potentially carcinogenic compounds with a duration of treatment of ≤ 1 month

The SCT is appropriate. The following extractables were found at greater than 5 mcg/day.

Table 6. Summary of Detected Extractable Compounds Above Qualification Threshold (5 mcg/day)

Extractables		
Mfr equipment- (b) (4) **mixing bag and tubing**		
Name of the compound	Maximum concentration level (MCL) in extractable studies	
	mcg/day	ppb in the DP
Volatile		
(b) (4)	(b) (4)	(b) (4)
Semi-volatile		
Not detected	-	-
Non-volatile		
(b) (4)	(b) (4)	(b) (4)
Mfr equipment- (b) (4) **mixing bag and** (b) (4)		
Volatile		
Not detected	-	-
Semi-volatile		
Not detected	-	-
Non-volatile		
(b) (4)	(b) (4)	(b) (4)
(b) (4) **and** (b) (4) **cap/stopper**		
Volatile		
(b) (4)	(b) (4)	(b) (4)
Semi-volatile		
Not detected	-	-
Non-volatile		
Not detected	-	-

Leachable Studies

The Applicant completed leachable studies on multiple batches at T0, 6 months, and 12 months at 25°C / 40% relative humidity, and 6 months at 40°C / 25% relative humidity. The leachable study was adequately informed by the extractable study per the CMC review team (see CMC review). However, there were limitations in the limit of quantification (LOQ) for several targeted compounds. The results of the leachable study and the impacts of the LOQ limitations on the toxicological assessment are discussed below.

Table 7. Leachable Study Conditions

Timepoint	Batch Lots
T0	X0000085 X0000086 X0000087
6 month	X0000050 X0000051 X0000052 X0000085 X0000086 X0000087
12 month	X0000050 X0000051 X0000052

Table 8. Summary of Detected Leachable Compounds Above Qualification Threshold (5 mcg/day)

Leachables		
Name of the compound	Maximum concentration level (MCL) in leachable studies	
	mcg/day	ppb in the DP
Volatile		
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Semi-volatile		
Not detected	-	-
Non-volatile		
Not detected		

In the Applicant's leachable studies, two leachables were detected at greater than the recommended qualification threshold of 5 mcg/day ((b) (4) which were ethanol and (b) (4)

(b) (4). Maximum daily exposure – (b) (4) mcg/day

To address the safety of (b) (4) levels, the Applicant references ICH Q3C guidance on residual solvents, which applies to all dosage forms and routes of administration. In this guidance, (b) (4) is considered a Class 3 solvent which may be regarded as less toxic and of lower risk to human health and is associated with an acceptable daily intake of (b) (4). In addition, the Applicant submitted QSAR evaluation for (b) (4) which was

evaluated negative for mutagenicity. This Reviewer concurs with the Applicant that at the levels present in the drug product, (b) (4) is not a safety concern.

(b) (4)

Uncertainty factors (UFs)
F1 (extrapolation from rats to humans) = **5**
F2 (variability between individuals) = **10**
F3 (study exposure duration) = **1**
[Note that drug product exposure is acute and exposure in (b) (4) is 13 weeks]
F4 (lack of adequate reproductive and developmental assessments) = **10**
F5 (determination of NOAEL) = **1**
F6 (additional factor*) = **10**
*to account for potential differences in toxicity with inhalational route to intravenous route

Total UF= 5000

(b) (4)

Therefore, this Reviewer concludes that the (b) (4) levels detected as leachables in the drug product are not a safety concern.

During discussions with the CMC review team, several target compounds were associated with limits of quantification (LOQs) that were insufficient to accurately quantify below 5 mcg/day and a CMC IR was sent to the Applicant. The Applicant replied that for those compounds that had LOQ that was above 5 mcg/day were based on toxicological risk assessments with PDEs several fold higher than the LOQ. However, of the seven compounds that had higher LOQs than 5 mcg/day, six compounds were associated with Limit of Detection (LOD) that were lower than 5 mcg/day (as seen in the table below) and only (b) (4) was associated with a LOD that was higher than 5 mcg/day.

Compound	Limit of Detection (PPB)	Limit of Quantitation (PPB)
(b) (4)	(b) (4)	(b) (4)

Note: (b) (4) equates to 5 mcg/day

Given that the limit of detection of [redacted] is higher than 5 mcg/day, the product may contain levels up to [redacted] in the drug product and not be detected and therefore a toxicological risk evaluation of this compound by this Reviewer was conducted.

[redacted]). Maximum daily exposure [redacted] mcg/day

[redacted] is an organic acid that is used as a food additive and flavoring substance and is naturally present in a wide variety of foods. As stated in 21 CFR [redacted], [redacted] is generally recognized as safe (GRAS) when used in accordance with good manufacturing or feeding practice. To support the safety of the levels of [redacted], the Applicant cites an EFSA article that provides a scientific opinion of the safety of [redacted] The article states that [redacted] is an authorized food additive in the EU with maximal permitted level ranging from [redacted] mg/kg in foods and noted that [redacted] are naturally occurring substances in the diet. Absorption was described to be rapidly occurring and has been evaluated in rats and in humans. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an Acceptable Daily Intake (ADI) "not limited", which is no longer used as a term by JECFA. It has the same meaning as the current term "not specified" which is applicable to food substance of very low toxicity for which the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not represent a hazard to health. It is estimated that adult humans are exposed to [redacted] from natural sources based on dietary surveys to [redacted] mg/kg/day, which is about [redacted] for a 60 kg human (EFSA, 2014). While these dietary exposures are by the oral route, with even limited systemic uptake they are of much greater magnitude than the potential parenteral exposure to [redacted] with the drug product ([redacted]).

In summaries of the repeated dose toxicity studies cited by the EFSA publication, which the full publications could not be located by this Reviewer, administration of [redacted] in the diet resulted in acanthosis and hyperkeratosis of the forestomach mucosa in rats at concentrations of 0.62% with these lesions showing reversibility. In long-term studies, forestomach lesions were reported, however, the panel considered these rodent findings as not relevant because humans lack this organ and absence of correlation between forestomach in rats and esophageal lesions in humans. There are no reproductive toxicity studies with [redacted] but it is noted that the repeated dose studies did not report histopathological findings in reproductive organs. Developmental toxicity and maternal toxicity were not observed when rodents were tested up to [redacted] mg/kg, the highest dose tested.

Taken together, there are no concerns with the extractable/leachables data submitted for the container closure system.

Elemental Impurities

The drug product Lots X0000050, X0000051, X000052 (T0, 6M, 12M), and Lots X0000085, X0000086, X0000087 (T0, 6M) were tested for elemental impurities in the leachable studies. The Applicant referenced PDEs based on [redacted] rather than Q3D.

However, when this Reviewer compared the reported levels with Q3D limits, no elementals were detected above the PDEs specified in Q3D.

2.6 Proposed Clinical Population and Dosing Regimen

Ephedrine sulfate, 5 mg/mL in a prefilled syringe, is indicated for the treatment of clinically important hypertension in the setting of anesthesia. The recommended dosage is an initial dose of 5 to 10 mg administered by intravenous bolus. Additional intravenous boluses maybe administered to a maximum dose of 50 mg.

The dosing regimen is identical to the original approved product except that the original approved product (50 mg/mL) requires dilution before administration.

2.7 Regulatory Background

The original NDA 208289 was approved on April 29, 2016 for a 50 mg/mL ephedrine sulfate presentation, which requires dilution. The current prior approval supplemental is for a prediluted form of the drug product in a syringe. There were no additional meetings prior to the NDA 208289 S006 submission.

10 Special Toxicology Studies

Local Tolerance

The Applicant [(b) (4)] the range of the original approved product for this NDA. The Applicant [(b) (4)]. The [(b) (4)] for these would both be within the range of the referenced product but is about [(b) (4)] than the original product at the [(b) (4)] bound. Upon review of the available literature, this Reviewer agrees that the difference between the [(b) (4)] 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 [(b) (4)]). In this case, the [(b) (4)] of this standard treatment. In another publication, [(b) (4)] of whole blood samples collected from hospital patients were reported to have a range between [(b) (4)] with a mean of [(b) (4)] It is also noted that other intravenous solutions that are hypertonic are routinely administered intravenously (e.g., [(b) (4)] is used to treat severe, critical hyponatremia and dextrose solutions [(b) (4)] are used to treat hypovolemia). Another consideration for local safety is the rate of infusion of the solution. Studies in rabbits indicated that [(b) (4)] were better tolerated with acute dosing compared with longer infusions [(b) (4)]). In this study a [(b) (4)] 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 [(b) (4)] 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 resulted 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 (b) (4) should be infused at the highest rate clinically feasible as the data demonstrated that increasing infusion rates of (b) (4) 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 has been 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 (b) (4) in ephedrine is likely to be (b) (4) Taken together, the (b) (4) levels and other commonly used IV solutions, the dosing regimen is an acute bolus dose, and that administration of ephedrine (b) (4) is unlikely to raise any safety concerns.

11 Integrated Summary and Safety Evaluation

The Applicant (b) (4) the original approved product in NDA 208289 has an osmolality of 280-320 mOsm/kg. During the review process the Applicant was asked (b) (4) The Applicant committed to (b) (4) the original approved drug. The proposed (b) (4) and other commonly used IV solutions (See discussion above), the dosing regimen is an acute bolus dose, and the administration of ephedrine (b) (4) Therefore, the (b) (4) drug product and the reference product is unlikely to raise any safety concerns. From a nonclinical perspective (b) (4) is considered acceptable.

There are no safety concerns with the drug product formulation as there are no novel excipients. Specifications for drug substance and drug product impurities are acceptable as all the impurities do not exceed ICH Q3A and Q3B qualification thresholds. However, there was one unique drug product degradant that is not detected in the currently approved, more concentrated drug product, known as (b) (4) which is a Schedule I substance. The Applicant has set a specification of NMT than (b) (4) for this drug product degradant. From a nonclinical toxicology perspective, the specification is acceptable because the proposed specification is below the qualification threshold as described in ICH Q3B(R2) and that the maximum daily intake of 50 mcg/day does not raise any toxicological safety concerns. We defer to the Controlled Substance Staff

(CSS) regarding the acceptability and implications of the presence of this degradant in the drug product.

In the Applicant's leachable studies [redacted] and [redacted] were detected at greater than the requested qualification threshold of [redacted] (5 mcg/day); However, [redacted] levels were within the residual solvent limits outlined in Q3C and [redacted] levels were below an estimated PDE calculated by this Reviewer. Although several compounds were associated with higher Limit of Quantitation values, the Limit of Detection for these compounds were below the 5 mcg/day qualification threshold with the exception of [redacted]. Both the LOQ and LOD were above the 5 mcg/day and therefore a risk assessment was conducted on the LOD value of [redacted] As [redacted] is commonly found in food at much higher levels and is fairly bioavailable, the levels that a subject would be exposed to is associated with low risk. Therefore, there are no safety concerns regarding leachables in the drug product.

From a nonclinical pharmacology toxicology perspective, NDA 208289 prior approval supplement for the 5 mL syringe may be approved.

12 Appendix/Attachments

References

EPA (2009). "Provisional Peer-Reviewed Toxicity Values for [redacted] Environmental Protection Agency, Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Office of Research and Development, EPA/[redacted]
https://cfpub.epa.gov/ncea/pprtv/documents/[redacted]

[redacted]

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/s/

CASANDRA M CARTAGENA
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

OTHER REVIEW(S)

Division of Anesthesiology, Addiction Medicine, and Pain Medicine

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 208289/S-006

Name of Drug: Akovaz (ephedrine sulfate) injection

Applicant: Exela Pharma Sciences, LLC.

Labeling Reviewed

Submission/Receipt Dates: 11/10/20 (original)
3/10/21 (amended labeling)

Last Approved Label: 4/8/20 (sNDA-005)

Background and Summary Description

This is a CMC supplement that proposes a ready-to-use (pre-diluted) formulation of the product in a pre-filled syringe presentation.

The proposed labeling for the package insert (PI) was compared to the PI approved with the sNDA-005 on 4/8/20.

The reviews in Panorama/DARRTS dated 3/9, and 7/19/21, from OPQ, and the joint nonclinical review/Action Summary memo dated 7/22/21, recommending that this sNDA should be approved.

Also see the review in DARRTS dated 3/8, 3/9, and 6/4/21, by Cameron (Johnson) Clark of DMEPA stating DMEPA's initial IRs for labeling, the firm's compliance with them, and the acceptability of final C & C for this sNDA. Note that the DMEPA reviews discuss the newly proposed carton and container labeling for this new presentation. See that for discussion of the C & C labeling for this sNDA.

Review

The Sponsor proposes changes to sections **2 DOSAGE AND ADMINISTRATION, 3 DOSAGE FORMS AND STRENGTHS, 11 DESCRIPTION, AND 16 HOW SUPPLIED,** as well as updating the sponsor name and contact info throughout the PI. They do not propose changes to other portions of the PI.

The Sponsor has submitted carton and container labeling for their new presentation and as note above DMEPA has reviewed those materials.

Additions to the PI when compared with the last approved label are shown below in colored underline (purple for Sponsor-proposed, and green for Agency proposed). Deletions are shown in colored ~~strikeout~~ (~~purple~~ for Sponsor-proposed, and ~~green~~ for Agency proposed).

Package Insert

I. Highlights

In the PRODUCT TITLE, the Division requested that the Sponsor remove "USP" from the established name of the product:

> AKOVAZ (ephedrine sulfate injection~~, USP~~) for intravenous use
> Initial U.S. Approval: 2016

In the DOSAGE AND ADMINISTRATION Section of Highlights, the Sponsor proposed to add bullets #1 and 3 and update the references to the corresponding sections of the FPI:

- Should be administered by trained healthcare providers (2.1)
- AKOVAZ injection, 50 mg/mL [redacted (b) (4)]. (2.1)
- AKOVAZ injection, 5 mg/mL in a pre-filled syringe, [redacted (b) (4)] is a premixed formulation. Do not dilute prior to use. (2.1)
- Bolus intravenous injection: 5 to 10 mg as needed, not to exceed 50 mg. (2.1)

The Agency requested the following changes, noting that equivalency statements are not needed in the Highlights Section:

- Should be administered by trained healthcare providers (2.1)
- AKOVAZ injection, 50 mg/mL, [redacted (b) (4)] must be diluted before administration as an intravenous bolus dose [redacted (b) (4)] (2.1)
- AKOVAZ injection, 5 mg/mL in a pre-filled syringe, [redacted (b) (4)] is a premixed formulation. Do not dilute prior to use. (2.1)
- Bolus intravenous injection: 5 [redacted (b) (4)] to 10 mg as needed, not to exceed 50 mg. (2.1)

Via an email exchanges with the Sponsor on 3/5, 3/8, and 3/9/21 the Sponsor has agreed to these changes.

In the DOSAGE FORMS AND STRENGTHS Section of Highlights, the Sponsor proposed to add the following:

> Injection: 50 mg/mL ephedrine sulfate in single-dose vial and 25 mg/5 mL (5 mg/mL) ephedrine sulfate in a 5 mL single-dose prefilled syringe (3)

In the ADVERSE REACTIONS Section of Highlights, the name of the firm and contact phone number for reporting adverse events was updated to the current Sponsor:

To report SUSPECTED ADVERSE REACTIONS, contact ~~Avadel at 1-877-638-4579~~ Exela Pharma Sciences, LLC at 1-888-451-4321 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

These changes are acceptable to the Agency.

II. Table of Contents

The Sponsor added Subsection 2.4 Instructions for Use of Prefilled Syringe to **DOSAGE AND ADMINISTRATION.**

These changes are acceptable to the Agency.

III. Full Prescribing Information

In the **2.1 General Dosage and Administration Instructions** subsection of the **Section 2 DOSAGE AND ADMINISTRATION**, the Sponsor proposed the following changes:

AKOVAZ (ephedrine sulfate injection), 50 mg/mL must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.

AKOVAZ (ephedrine sulfate injection), (b) (4) .

The Agency proposed the following addition:

AKOVAZ (ephedrine sulfate injection), 25 mg/5 mL (5 mg/mL) in a prefilled syringe, is a premixed formulation. Do not dilute prior to use. The single-dose prefilled syringe is intended for use in one patient during one surgical procedure. Discard any unused portion.

Via an email exchanges with the Sponsor on 3/5, 3/8, and 3/9/21 the Sponsor has agreed to these change.

In the **2.2 Dosing for the Treatment of Clinically Important Hypotension in the Setting of Anesthesia** subsection of **DOSAGE AND ADMINISTRATION,** the Sponsor proposed adding the following text as the first line in the section:

AKOVAZ should be administered by trained healthcare providers.

The above change is acceptable, and the Agency requested that the Sponsor add the unit of measure to the lower dose in the dosage range here as well:

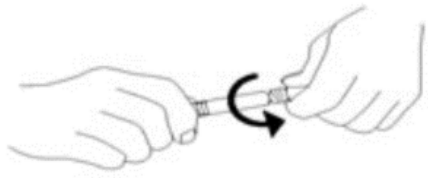
The recommended dosages for the treatment of clinically important hypotension in the setting of anesthesia is an initial dose of 5 mg to 10 mg administered by intravenous bolus. Administer additional boluses as needed, not to exceed a total dosage of 50 mg.

The Sponsor agreed to this change.

The Sponsor proposed adding subsection **2.4 Instructions for Use of Prefilled Syringe** to the **DOSAGE AND ADMINISTRATION** section with the following text and graphic:

1. Perform visual inspection on the syringe by verifying:
- Absence of syringe damage
- Absence of external particles
- Absence of internal particles
- Proper drug color
- Drug name
- Drug strength
- Fill volume
- Route of administration
- Expiration date to be sure the drug has not expired

2. Do not remove the tamper evident seal. Push plunger rod slightly in to break the stopper loose while tip cap is still on.
3. Remove tip cap and tamper evident seal by twisting off. (See Figure 1):
Figure 1.



4. Discard the tip cap.
5. Expel air bubble.
6. Adjust dose into sterile material (if applicable).
7. Connect the syringe to an appropriate intravenous connection.
Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).
8. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.
9. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle.
To prevent needle stick injuries, do not recap needle when needle is connected to syringe.
NOTES:

All steps must be done sequentially
- Do not re-sterilize syringe
- Do not use this product on a sterile field
- Do not introduce any other fluid into the syringe at any time
- This product is for single dose only

All changes were acceptable to the Agency aside from requesting that the Sponsor remove the "s" from "notes" (as indicated above by green strikeout.) The Sponsor agreed to this change.

In **Section 3 DOSAGE FORMS AND STRENGTHS**, the Sponsor proposed the below-underlined text to indicate the new presentation:

AKOVAZ (ephedrine sulfate injection) [redacted] (b) (4) .

The Agency requested the following changes, breaking out the 2 presentations into their own lines:

[redacted] (b) (4)

The Division also requested that the Sponsor add a description of identifying characteristics of the dosage forms. The Sponsor accepted the above changes and added the requested description so the agreed upon Section 3 now appears:

AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection available as:

single-dose 1 mL vial that contains 50 mg/mL ephedrine sulfate, equivalent to 38 mg/mL of ephedrine base

single-dose 5 mL prefilled syringe that contains 25 mg/ 5 mL (5 mg/mL) ephedrine sulfate equivalent to 19 mg/5 mL (3.8 mg/mL) of ephedrine base

The final proposed form is acceptable to the Agency.

In **Section 11 DESCRIPTION**, the Sponsor proposed deleting the 2nd sentence in the 1st paragraph:

> Ephedrine is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection. [redacted]

The Sponsor proposed expanding what was previously the 2nd paragraph into a new 2nd, 3rd, and 4th paragraph as follows:

> Ephedrine sulfate is freely soluble in water and ethanol, very slightly soluble in chloroform, and practically insoluble in ether.
>
> Each mL of the 50 mg/mL strength contains ephedrine sulfate 50 mg (equivalent to 38 mg ephedrine base) in water for injection. The pH is adjusted with sodium hydroxide and/or glacial acetic acid if necessary. The pH range is 4.5 to 7.0. The 50 mg/mL vial must be diluted before intravenous administration.
>
> Each mL of the 5 mL single-dose prefilled syringe contains 5 mg ephedrine sulfate (equivalent to 3.8 mg ephedrine base) and 9 mg Sodium Chloride, USP in Water for Injection. The pH range is 4.5 to 6.5.

These changes are acceptable to the Agency.

In **Section 16 HOW SUPPLIED/STORAGE AND HANDLING**, the Sponsor proposed changing the following changes to update the new NDC #s to reflect the current sponsor and adding the new presentation to the chart:

AKOVAZ (ephedrine sulfate injection), [redacted]:

NDC	Strength	How Supplied
[redacted] 51754-4200-4	[redacted]	1 mL clear glass vial; for single-dose (supplied in packages of 25)
51754-4250-3		5 mL single-dose prefilled syringe (supplied in packages of 10)

The **Agency requested** that the Sponsor add a description of identifying characteristics of the dosage forms to Section 16 as in Section 3, requested insertion of equivalency information and a representation of the full amount available in the presentation, and addition of the statement that the prefilled product is intended to be used only on one patient for one case. **The Sponsor agreed to these changes** and Seciton 16 now appears as follows:

> AKOVAZ (ephedrine sulfate injection) is a clear, colorless, sterile solution for intravenous injection supplied as follows:

NDC	Strength	How Supplied
51754-4200-4	50 mg/mL of ephedrine sulfate equivalent to 38 mg/mL of ephedrine base	1 mL clear glass vial; for single-dose (supplied in packages of 25)

51754-4250-3	25 mg/ 5 mL (5 mg/mL) of ephedrine sulfate equivalent to 19 mg/5 mL (3.8 mg/mL) of ephedrine base	5 mL single-dose prefilled syringe (supplied in packages of 10)

Vial stoppers are not manufactured with natural rubber latex. Store AKOVAZ (ephedrine sulfate injection), at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in carton until time of use. For single dose only. Discard unused portion.
The single-dose 5 mL prefilled syringe is intended for use in one patient during one surgical procedure.

Although updated outside of a supplement the NDA Sponsor has changed since the labeling for S-005 was approved and so there is new manufacturing information in the PI reflected here that was not in S-005:

Avadel

~~Avadel Legacy Pharmaceuticals, LLC~~

~~Chesterfield, MO 63005~~

EXELA PHARMA SCIENCES

Exela Pharma Sciences, LLC
Lenoir, NC 28645

There were no other changes to the PI.

Recommendations

As the Sponsor and Agency have reached agreement on proposed changes in the labeling and as recommended by the nonclinical and chemistry team in their finalized reviews, this sNDA should be approved.

Kimberly Compton, Senior Regulatory Project Manager, 2/23/21, updated 3/10/21

Matt Sullivan, MS, Chief, Project Management Staff, 7-19-21

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/s/

KIMBERLY A COMPTON
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 4, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 208289/S-006
Product Name and Strength:	Akovaz (ephedrine sulfate) injection, 25 mg/5 mL (5 mg/mL)
Applicant/Sponsor Name:	Excela Pharma Sciences LLC
OSE RCM #:	2021-2676-2
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on May 28, 2021 for Akovaz. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised carton labeling for Akovaz (Appendix A) to determine if it is acceptable from a medication error perspective. The Applicant previously submitted the revised container label and carton labeling in response to our previous recommendations and we found the revised labeling acceptable from a medication error perspective.[a] In this recent submission[b], the Applicant noted that the ingredients statement on the carton labeling for the syringe presentation has been revised.

2 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Akovaz (NDA 208289/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 09. RCM No.: 2021-2676-1.
[b] Labeling Update Cover Letter (Akovaz NDA 208289/S-006). Linoir (NC): Excela Pharma Sciences LLC; 2021 MAY 28. Available from: \\CDSESUB1\evsprod\nda208289\0076\m1\us\12-cover-letters\cover-letter-0076.pdf

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 9, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 208289/S-006
Product Name and Strength:	Akovaz (ephedrine sulfate) injection, 25 mg/5 mL (5 mg/mL)
Applicant/Sponsor Name:	Excela Pharma Sciences LLC
OSE RCM #:	2021-2676
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Associated Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 8, 2021 for Akovaz. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Akovaz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ANALYSIS AND DISCUSSION

Exela included in their response, to our container label and carton labeling recommendations[a], that the (b) (4) ” on the carton labeling and will include the required product identifier information as indicated by the example shown in Figure 1 below:

[a] Johnson, C. URRA, CA, and Label and Labeling Review for Akovaz (NDA 208289/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 05. RCM No.: 2021-69 and 2021-2676.

(b) (4)

3 CONCLUSION

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

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/s/

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LOLITA G WHITE
03/09/2021 09:16:25 AM

USE-RELATED RISK , COMPARATIVE ANALYSIS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 5, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 208289/S-006
Product Name and Strength:	Akovaz (ephedrine sulfate) injection, 50 mg/mL vial 25 mg/5 mL (5 mg/mL) prefilled-syringe *(proposed)*
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Excela Pharma Sciences LLC
FDA Received Date:	November 10, 2020
OSE RCM #:	2021-69 and 2021-2676
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Excela Pharma Sciences LLC submitted a prior approval supplement for Akovaz (ephedrine sulfate) injection to propose an additional product presentation, a 25 mg/5 mL (5 mg/mL) single-dose prefilled syringe (PFS). Subsequently, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Akovaz prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors. Additionally, we evaluated the submitted use-related risk analysis (URRA), comparative analysis, and justification to determine whether the Applicant needs to submit the results of a human factors (HF) validation study as part of this NDA supplement.

This is a combination product with a proposed PFS device constituent part that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

1.1 Product Description

The proposed 25 mg/5 mL prefilled syringe is comprised of a plunger, stopper, barrel, luer lock and tip cap (see Figure 1 below). The tip cap is covered with a tamper evident seal. As described in the URRA, Akovaz is intended to be injected intravenously by trained healthcare providers (HCPs), such as anesthesiologists or surgical nursing staff members in the setting of anesthesia. Akovaz is administered using a 25 mg/5 mL syringe and dosed as an initial bolus of 5 mg to 10 mg followed by additional boluses as needed not to exceed a total dosage of 50 mg. The dosage of the product is closely monitored by these HCPs, and the doses are titrated for each individual patient. Table 4 in Appendix A contains additional product details.

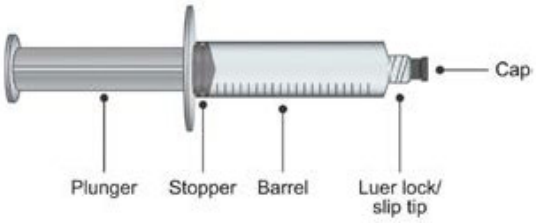

Figure 1: Graphical Depiction of the User Interface

2 REGULATORY HISTORY

Akovaz (NDA 208289) was approved on April 29, 2016 for the 50 mg/mL single-dose vial presentation.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Use-related Risk Analysis (URRA)	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 ASSESSMENT OF TOTAL PRODUCT STRENGTH AND PACKAGE TYPE TERM

During our initial review of the labels and labeling, we noted that the proposed product is labeled with the package type term "single dose" and that the strength, 25 mg/5 mL, is incongruent with the Dosage and Administration section of the PI which recommends initial doses of Akovaz 5 mg to 10 mg. As a single dose container closure, the proposed strength of the PFS may result in 15 mg to 20 mg (3 mL to 4 mL) of waste if a user adjusts for the dose by discarding excess drug then administering the 5 mg or 10 mg dose. There is also a risk associated with the entire contents of the 25 mg syringe being administered at once if the user does not discard excess first before administering. PFS are typically single dose and "the safest practice is for syringe and needle to be used only once to administer a medication to a single patient, after which the syringe and needle should be discarded. This practice prevents inadvertent reuse of the syringe and protects healthcare personnel from harm such as needle stick injuries." [a]

However, we note that in the setting of anesthesiology, the administration of ephedrine sulfate doses is titrated to effect. It is customary for incremental doses to be administered using the

[a] Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP), June 20, 2019. Available from:

https://www.cdc.gov/injectionsafety/providers/provider_faqs_med-admin.html#anchor_1561047533

same syringe. For example, for the currently marketed 50 mg/mL single dose vials of ephedrine sulfate, the entire contents of the vial are diluted to a final drug concentration of 50 mg/10 mL (5 mg/mL) and the diluted solution is drawn up in a syringe. The syringe is then used by the healthcare provider to give incremental doses, 5 mg (1 mL) to 10 mg (2 mL) at a time, while titrating to effect until goal blood pressure is reached. Thus, based on the clinical use of ephedrine sulfate products in the setting of anesthesia, we considered whether "single patient use" would be the appropriate package type term.

We sought input from the Office of Policy for Pharmaceutical Quality (OPPQ) regarding the appropriate package type term for this PFS (i.e. single dose or single patient use). OPPQ was concerned that labeling this PFS as "single patient use" would be setting a precedent and that this is not typical for prefilled syringes. However, given the very specific setting of use and after further discussions with the DAAP review team (i.e. clinical, chemistry, microbiology), OPPQ proposed including the package type term as "single dose" with additional information to describe appropriate use in the setting of anesthesia. OPPQ proposed to include the following statement on the labels and labeling:

> "The single-dose prefilled syringe is intended for use in one patient during one surgical procedure".

After discussions with the DAAP clinical team regarding the use of ephedrine sulfate in the setting of anesthesia, we note that users are familiar with and aware of the use of ephedrine sulfate in a syringe in this manner. While it's possible that introduction of the "single dose" package type term on a product that is intended to be used for multiple doses in a single patient may cause some initial confusion when first introduced to the market, we determined that it's unlikely to introduce a new risk that would preclude this strategy. We ultimately defer to OPPQ regarding the determination of package type term.

5 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	In the Dosage and Administration section of the Highlights and Full Prescribing Information, the (b) (4)	Omission of the units of measure, could result in wrong dose errors or result in the lower dose in the	We recommend adding the unit of measure, "mg", after the numeral "5" so that the statement reads:

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	dosage range to be overlooked.	"5 mg to 10 mg".
2.	The product strength for the prefilled syringe is not consistently expressed in the Highlights and Full Prescribing Information (FPI). For example, the product strength is expressed as (b) (4)	Inconsistent labeling may contribute to confusion that can result in a medication error. Furthermore, United States Pharmacopeia (USP) General Chapter <7> Labeling, recommends the strength be presented as total quantity per total volume followed by quantity per milliliter in parentheses.[b]	Revise the strength presentation for the prefilled syringe throughout all labels and labeling so that it reads as: 25 mg/5 mL (5 mg/mL)
Full Prescribing Information – Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling			
1.	The Dosage Forms and Strengths section and How Supplied/Storage and Handling section does not include information about the (b) (4) .	This important information facilitates the identification of the dosage form and is required for the Dosage Forms and Strengths section per 21 CFR 201.57(c)(4)(ii). Furthermore, this information should be included in the How	We defer to the Office of Pharmaceutical Quality (OPQ) to inform the Applicant to include that the drug product is a clear, colorless, sterile solution to both these sections.

[b] United States Pharmacopeia (USP) General Chapter <7> Labeling.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Supplied section per 21 CFR 201.57(c)(17).	
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The total quantity per total volume has not been included. The strength is (b) (4)	United States Pharmacopeia (USP) General Chapter <7> Labeling, recommends the strength be presented as quantity per total volume followed by quantity per milliliter in parentheses.[c]	Revise the strength to include the total quantity per total volume: 25 mg/5 mL (5 mg/mL)

Table 3. Identified Issues and Recommendations for Excela Pharma Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The route of administration is included as (b) (4)	Presenting the route of administration as an abbreviation may lead to misinterpretation of the correct route of administration.	Revise (b) (4) to the intended meaning, "For intravenous use".
Carton Labeling			
1.	As currently presented on the side panel, the statement (b) (4)	The (b) (4) could result in a ten-fold misinterpretation (b) (4) resulting in wrong strength, concentration,	To avoid a ten-fold misinterpretation, we recommend the removal of (b) (4) g Ephedrine Sulfate…".

[c] United States Pharmacopeia (USP) General Chapter <7> Labeling.

Table 3. Identified Issues and Recommendations for Excela Pharma Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	and/or wrong dose medication errors[d].	
2.	As currently presented, the (b) (4) for the lot number (b) (4) on the proposed carton labeling that was submitted.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1).	Include the space notation for the lot number statement. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number that can be mistaken as the lot number.
3.	As currently presented, the (b) (4) for the expiration date (b) (4) on the proposed carton labeling that was submitted.	The product expiration date is required on the carton labeling per 21 CFR 201.17.	Include the space notation for the expiration date. When determining this placement, please ensure that there are no other numbers located in close proximity to the expiration date that can be mistaken as the expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the container labels and carton labeling include a year, month, and non-zero day.

[d] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 FEB 27]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 3. Identified Issues and Recommendations for Excela Pharma Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	As currently presented, the (b) (4) on the smallest saleable unit (usually the carton) is not provided.	The drug package label must include the product identifier information (i.e., the NDC, serial number, lot number, and expiration date) in both the human-readable form and machine-readable, 2D data matrix barcode format.	We recommend you include the intended location of the machine-readable, 2D data matrix barcode product identifier, near the human-readable portion of the product identifier information. For more information, see draft guidance, Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers (September 2018).[e]

[e] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

6 USE-RELATED RISK ANALYSIS (URRA)

The Applicant submitted a URRA and Comparative Analysis (CA), to support their determination that the results of a HF validation study do not need to be submitted for their proposed product, Akovaz (ephedrine sulfate) Injection, 25 mg/5 mL (5 mg/mL) single-dose prefilled syringe.

Our review focused on the URRA for the proposed product and we agree that the tasks evaluated are comprehensive and appropriate for the proposed product. We also reviewed the URRA to ensure that all potential use errors and risks involved in using the proposed product, including known use issues with currently marketed products, have been considered and adequately mitigated. In addition, we did not identify any new, differing, or unique risks for the proposed product related to the user interface design as compared to other approved pre-filled syringes intended for use by healthcare professionals in the setting of anesthesia.

7 COMPARATIVE ANALYSES

Excela identified the currently marketed Fresenius product as a comparator product and performed a labeling comparison, a comparative task analysis, and a physical comparison.

Excela determined that the labeling is similar in all aspects and both labels state that the product should be administered by a trained healthcare professional. The only substantial physical difference is the packaging and corresponding labeling. We agree with the Applicant's determination and do not expect the identified differences to impact critical tasks nor the user's ability to use the product safely and effectively.

8 CONCLUSION

Based on our review of the URRA and CA for Akovaz (ephedrine sulfate) Injection, 25 mg/5 mL (5 mg/mL) single-dose prefilled syringe, intended for use by healthcare providers (HCPs), such as anesthesiologists or surgical nursing staff members, we determined that no additional HF data is needed at this time.

Additionally, our evaluation of the proposed Akovaz prescribing information (PI), container label, and carton labeling, identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Excela Pharma Sciences LLC so that recommendations are implemented prior to approval of this NDA Supplement.

8.1 RECOMMENDATIONS FOR EXCELA PHARMA SCIENCES LLC

We note your proposed product is a pre-filled syringe intended for use by healthcare professionals. In this particular instance, we determined that you do not need to submit results of a Human Factors (HF) validation study as part of the NDA Supplement.

Additionally, our review of the labels and labeling identified areas of vulnerability that may lead to medication errors. We provide these recommendations in Table 3 and we recommend that you implement these recommendations.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Akovaz that Excela Pharma Sciences LLC submitted on November 10, 2020, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Akovaz		
Product Name	Akovaz	Akovaz
Initial Approval Date	April 29, 2016	N/A
Active Ingredient	Ephedrine sulfate	
Indication	an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia	
Route of Administration	Intravenous bolus	
Dosage Form	injection	
Strength	50 mg/mL	25 mg/5 mL (5 mg/mL)
Dose and Frequency	• 5 mg to 10 mg intravenous bolus as needed not to exceed 50 mg • Must be diluted prior to administration	• 5 mg to 10 mg intravenous bolus as needed not to exceed 50 mg • Premixed formulation. Do not dilute.
How Supplied/Container closure	Packages of 25 single-dose vials	Packages of 10 single-dose prefilled syringes
Storage	USP Controlled Room Temperature	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 22, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Akovaz and 208289. Our search identified three previous reviews[f,g,h], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX E. Use-Related Risk Analysis (URRA) and Comparative Analysis (CA)

\\CDSESUB1\evsprod\nda208289\0067\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\urra-prefilled-syringe\urra-prefilled-syringe-0067-s006.pdf

[f] Schlick, J. Label and Labeling Review for Akovaz (NDA 208289). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 17. RCM No.: 2015-1556.

[g] Schlick, J. Label and Labeling Review Memo for Akovaz (NDA 208289). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 29. RCM No.: 2015-1555-1.

[h] Shah, M. Postmarket Review for Akovaz and Adrenalin (NDA 208289 and NDA 204640). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 10. RCM No.: 2016-2631.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Akovaz labels and labeling submitted by Excela Pharma Sciences LLC received on November 10, 2021.

- Container label
- Carton labeling
- Prescribing Information (Image not shown) can be accessed in EDR via the following link:
    - o \\CDSESUB1\evsprod\nda208289\0067\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-word-tc-0067.doc

F.2 Label and Labeling Images

Container label(s)

Carton labeling

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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LOLITA G WHITE
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IRENE Z CHAN
03/08/2021 08:56:59 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 2, 2021
Application Type and Number:	NDA 208289/S-006
Product Name and Strength:	Akovaz (ephedrine sulfate) injection, 5 mg/mL
Total Product Strength:	25 mg/5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC (Exela)
PNR ID #:	1044723773
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Director (Acting):	Lubna Merchant, MS, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Akovaz, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. We previously reviewed an external name study, conducted by (b) (4), for this proposed proprietary name.

1.1 REGULATORY HISTORY

Exela previously submitted the proposed proprietary name, Akovaz, on July 1, 2015 for the 50 mg/mL strength presentation that does not require dilution prior to administration. On August 28, 2018 we found the name, Akovaz, acceptable.[a]

On November 10, 2020, Exela submitted a prior approval supplement for the addition of the 25 mg/5 mL (5 m/mL) strength presentation of the drug product. However, the Applicant did not submit a request for proprietary name review for the new presentation. Therefore, on January 19, 2021 we sent an Information Request (IR)[b] to Exela requesting that they submit a request for proprietary name review if they intend to have a proprietary name for the proposed prefilled syringe presentation.

Thus, Exela submitted the name, Akovaz, for review on January 22, 2021.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on January 22, 2021.

Table 2. Relevant Product Information for Akovaz

Concentration	5 mg/mL (proposed)	50 mg/mL (approved)
Application Number	NDA 208289	
Intended Pronunciation	Ack-ho-vaz	
Active Ingredient	ephedrine sulfate	
Indication	an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia	
Route of Administration	Intravenous bolus	
Dosage Form	injection	
Strength	25 mg/5 mL (5 mg/mL)	50 mg/mL

[a] Schlick, J. Proprietary Name Review for Akovaz (NDA 208289). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 28. Panorama No. 2015-887601.

[b] White, Tamika. NDA 208289 S-006 Proprietary Name Information Request. Silver Spring (MD): FDA, CDER, OSE (US); 2020 JAN 19. NDA 208289 S-006.

Dose and Frequency	• 5 mg to 10 mg intravenous bolus as needed not to exceed 50 mg • **Premixed formulation. Do not dilute.**	• 5 mg to 10 mg intravenous bolus as needed not to exceed 50 mg • **Must be diluted prior to administration**
How Supplied	Packages of 10 single-dose prefilled syringes	Packages of 25 single-dose vials
Storage	USP Controlled Room Temperature	

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Akovaz.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Akovaz would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) concurred with the findings of OPDP's assessment for Akovaz.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Akovaz.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[c].

2.2.2 Components of the Proposed Proprietary Name

Exela did not provide a derivation or intended meaning for the proposed proprietary name, Akovaz, in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, February 5, 2021 e-mail, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not forward any comments or concerns relating to Akovaz at the initial phase of the review.

[c] USAN stem search conducted on February 10, 2021.

2.2.4 Safety Assessment of Multiple Formulations/Container Closures Under the Same Proprietary Name

Akovaz (ephedrine sulfate) injection, 50 mg/mL available as a vial was approved on April 29, 2016. It is not uncommon to have a product line with multiple formulations and container closures share one proprietary name, particularly when the different formulations/container closures are bioequivalent, which applies in this case. While we note that the strengths (50 mg/mL vs. 5 mg/mL), preparation instructions (requires dilution prior to administration vs. pre-mixed formulation that does not require dilution prior to administration), and container closure (vial vs. prefilled syringe) differ, these differences can be managed via labeling. We note that both formulations have the same active ingredient, route of administration, dosing, and indication. Additionally, the Applicant intends to market these two products under one prescribing information. Furthermore, based on our postmarket surveillance activities, we are not aware of any medication errors involving proprietary name confusion with Akovaz. Therefore, we find that marketing ephedrine sulfate injection, 25 mg/5 mL (5 mg/mL) in a prefilled syringe under the same proprietary name, Akovaz, is an acceptable naming strategy.

2.2.5 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) via e-mail on February 23, 2021. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on February 26, 2021, they stated no additional concerns with the proposed proprietary name, Akovaz.

3 CONCLUSION

The proposed proprietary name, Akovaz, is acceptable.

If you have any questions or need clarifications, please contact Tamika White, OSE project manager, at 301-796-0310.

3.1 COMMENTS TO EXELA PHARMA SCIENCES, LLC

We have completed our review of the proposed proprietary name, Akovaz, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on January 22, 2021, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [d]

[d] National Coordinating Council for Medication Error Reporting and Prevention. https://www nccmerp.org/about-medication-errors Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.

- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[e]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign

[e] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

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Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208289/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 208289/S-006

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Exela Pharma Sciences, LLC
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

ATTENTION: Aruna Koganti, PhD, MBA
Vice President Regulatory Affairs and Clinical Programs

Dear Dr. Koganti:

Please refer to your supplemental new drug application (sNDA) dated and received November 10, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection.

We also refer to your correspondence, dated and received January 22, 2021, requesting review of your proposed proprietary name, Akovaz.

We have completed our review of the proposed proprietary name, Akovaz and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 22, 2021, submission are altered prior to approval of the supplemental marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1]

- *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*[2]

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Tamika White, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0310. For any other information regarding this application, contact Kimberly Compton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS
03/05/2021 02:37:27 PM

NDA 208289/S-006

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Exela Pharma Sciences, LLC
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Attention: Aruna Koganti
Vice President Regulatory Affairs and Clinical Programs

Dear Ms. Koganti:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 208289

SUPPLEMENT NUMBER: S-006

PRODUCT NAME: Akovaz (ephedrine sulfate injection, USP)

DATE OF SUBMISSION: November 10, 2020

DATE OF RECEIPT: November 10, 2020

This supplemental application proposes to add a new presentation of ready-to-use Akovaz 25 mg/5mL (5 mg/mL) prefilled in a 5 mL [redacted (b) (4)] syringe.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 9, 2021 in accordance with 21 CFR: 314.101(a).

If the application is filed, the user fee goal date will be on March 10, 2021.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

If you have questions, please contact Kimberly Compton, RPh, RAC Senior Regulatory Project Manager via phone at 301-796-1191 or email at Kimberly.Compton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jane Mun, PharmD
Regulatory Project Manager
Anesthesiology, Addiction Medicine, and
Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

JANE J MUN
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