CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208289Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia and Analgesia Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	April 29, 2016
From	Rigoberto Roca, M.D. Deputy Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Deputy Division Director Summary Review
NDA Number	208289
Applicant Name	Flamel Ireland Limited
Date of Original Submission	June 30, 2015
PDUFA Goal Date	April 30, 2016
Proprietary Name / Established (USAN) Name	Akovaz (ephedrine sulfate) injection
Dosage Forms / Strength	50 mg/mL
Proposed Indication	Treatment of clinically important hypotension in the setting of anesthesia
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
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OPQ Review	Nandini Bhattacharya, PhD; Christina Capacci-Daniel, PhD; Nallaperumal Chidambaram, PhD; Donna Christner, PhD; Christopher Hough, PhD; Yaodong Huang, PhD; Steven Kinsley, PhD; Kelly Kitchens, PhD; Vidula Kolhatkar, PhD; Jeffrey Medwid, PhD Julia Pinto, PhD; Paul Perdue, PhD; Quallyna Porte, PhD; Bryan S. Riley, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD; Yun Xu, PhD
Pharmacology/Toxicology Review	Marcus Delatte, PhD; Newton Woo, PhD; Dan Mellon, PhD
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Project Management Staff	Ayanna Augustus, PhD; Parinda Jani

DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
DVP II = Division of Pharmacovigilance II
OND = Office of New Drugs
OPDP = Office of Prescription Drug Promotion
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Flamel Ireland Limited, has submitted a 505(b)(2) new drug application (NDA) for ephedrine sulfate. It is formulated as sterile aqueous solution for injection and is intended to be administered through the intravenous route. The proposed indication is treatment of clinically important hypotension in the setting of anesthesia. The Applicant has opted to reference only published literature in support of this application; no clinical studies were conducted by the Applicant.

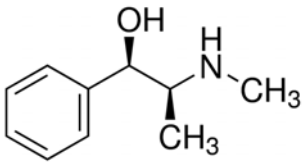
This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant. This review will also serve as the CDTL review.

2. Background

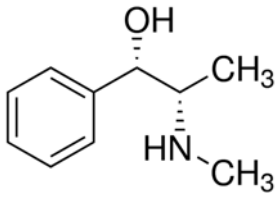
Ephedrine is a sympathomimetic agonist that binds to the α- and ß-adrenergic receptors. In addition to direct interaction with the adrenergic receptors, ephedrine can also have indirect effects by causing the release of endogenous catecholamines and/or by preventing their neuronal reuptake. These effects are manifested clinically as an increase in heart rate and cardiac output, and variable increases in peripheral vasculature resistance, resulting in an increase in systemic blood pressure. Ephedrine has been used clinically as a vasopressor for decades; however, it is currently a marketed, unapproved product.

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

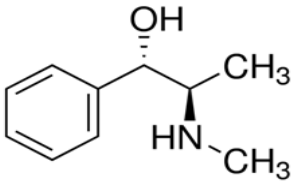
(1R,2S)-(-)Ephedrine



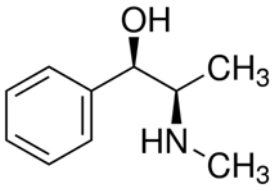
(1S,2S)-(+)Pseudoephedrine



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



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



As noted by the chemistry team in their reviews, the (-)-(1R,2S)–enantiomer of ephedrine cannot convert to (+)-(1R,2S)- enantiomer of ephedrine due to steric hindrance. However, the stereoisomers differ from each other with respect to their relative efficacy. Therefore, it was important that the Applicant establish with as much certainty as possible, the isomeric

structure of the ephedrine used in the clinical trials being reported in the published literature being used to support the NDA. With respect to the salt that was used in the clinical trial (i.e., ephedrine sulfate or ephedrine hydrochloride), the Division concluded that either one would be supportive.

Regulatory History

The regulatory history of this application is well-summarized in Dr. Luckett's review. The following table, adapted from Dr. Luckett's review, lists the key clinical issues identified during the meetings:

Meeting/ Date	Key clinical issues
PIND Type B/ December 19, 2012	1. Provide rationale for extrapolating data in parturients to ephedrine's total patient population 2. A clinical trial will be necessary if the literature you provide is not adequately supportive. 3. Confirm that the enantiomeric composition of your drug product is the same as that in the literature you submit 4. The sponsor will try to obtain clinical data sets and protocols from literature authors.
EOP2 Type B/ November 19, 2013	1. The applicant's ability to reference published literature depends on verification of the form of ephedrine used in the clinical studies to be relied upon. 2. The applicant must demonstrate that purity of drug product did not change over the study period. 3. A clinical trial will be necessary if the literature you provide is not adequately supportive. A trial would need to study ephedrine in the setting of neuraxial and general anesthesia. 4. Indication for ephedrine should not be too narrow (i.e., include only the treatment of hypotension in women over the age of 18 having neuraxial anesthesia for cesarean delivery). 5. The proposed indication of (b) (4) of hypotension 6. Describe your efforts to obtain study data in your NDA. 7. Organize clinical information by type of anesthesia, surgical procedure, and method of administration 8. Pediatric studies should not be waived.
Guidance Type C/ April 9, 2014	1. Studies with ephedrine hydrochloride can also be used to support your application. 2. Provide rationale for using foreign data. 3. Provide rationale that ephedrine provides clinical benefit other than raising blood pressure. 4. Dosing must be derived from those literature references in which the enantiomeric composition of ephedrine is appropriate.
Pre-NDA Type B/ April 23, 2015	1. The sponsor should compare the purity of their ephedrine with that of other currently manufactured ephedrine products. 2. Ephedrine hydrochloride can be used to support NDA for ephedrine sulfate. Will include tables in NDA submission to convert the strengths 3. The number of subjects receiving ephedrine under general anesthesia in the literature you plan to reference is relatively small. The adequacy of the data to support your indication will be a matter of review, but this lack of data will not be a filing issue and could potentially be addressed in product labeling. 4. If you submit studies in which ephedrine is used prophylactically, provide rationale for how this data will support the overall safety of

Meeting/ Date	Key clinical issues
	ephedrine. 5. Ephedrine sulfate is a List 1 chemical controlled by the DEA. Applicant should provide data to support the ephedrine dose, frequency of dosing, and maximum dose. 6. Applicant should address use of ephedrine in those with renal impairment.

It is worth noting that the importance of identification of the isomeric structure of the ephedrine used in the clinical trials reported in the literature was conveyed to the Applicant during several interactions. In the NDA submission, the Applicant indicated recognition that the literature could not be relied upon for evaluation of the efficacy if the study drug had not been identified as (-) ephedrine, either in the sulfate or the hydrochloride salt form. The Applicant has submitted information to address this issue, as noted below.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Drug Substance

The drug substance, ephedrine sulfate, USP, is supplied by (b) (4), and the manufacture and control is referenced to DMF (b) (4). The DMF was reviewed and found to be supportive for use in the preparation of the drug product.

Drug Product

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

> Ephedrine Sulfate Injection, USP is (b) (4) sterilized aqueous solution consisting of ephedrine sulfate and Water for Injection, USP. Either sodium hydroxide or glacial acetic acid is added (b) (4) for pH adjustment. The pH is controlled at approximately 5.0-5.5 and an osmolality of approximately 300 mOsmol/kg. The solution is (b) (4) The solution is filled into (b) (4) mL clear glass vials and closed with a pharmaceutical grade stopper (b) (4) and crimp seals. The vial is filled with (b) (4) of solution, which includes a slight overfill to allow for removal of 1.0 mL for dosing. (b) (4) The product is designed to meet Ephedrine Sulfate Injection USP monograph requirements. The drug product must be diluted with saline or 5% dextrose prior to administration. The product cannot be administered as a bolus injection.
>
> The granted expiry is 24 months when stored at 25C.

Facilities Reviews/Inspections

As noted in the OPQ review "A review of the manufacturing capability and inspectional documents of the manufacturing facilities listed above for NDA 208289 has been conducted. There are no significant, outstanding facility risks that prevent approval of this application. All of the noted facilities are found to be acceptable."

Product Quality Microbiology

There were several information requests sent to the Applicant by the OPQ review team during the course of the review. The information in the NDA submission, as well as the Applicant's

responses submitted on October 2, 2015 and March 11, 2016, resulted in an overall favorable assessment and recommendation for approval.

Specific Issues Identified in the Course of the Review

As noted above, the Division had informed the Applicant prior to the submission of the NDA that obtaining information to confirm the isomeric identity of the product used in the clinical trials that were described in the publications that were being used to support the NDA was critical.

In order to obtain this information, the Applicant utilized a variety of strategies to contact the author of the publications, the pharmacy at the hospital where the trial was conducted, and the manufacturer of the product that was used in the clinical trial. These efforts are summarized in the table below, adapted from the Applicant's submission.

Citation	Isomer (+/-)	Salt	Manufacturer	Contact History
Adigun et al. 2010	(-)	HCl	(b) (4)	Adigun TA indicated via email that he used ephedrine hydrochloride. Soyannwo OA indicated via email that the drug was from (b) (4) indicated via email that the drug consists of only the (-)isomer. Label states that API is Ephedrine Hydrochloride Ph Eur; the current Ph Eur monograph is for the (-)isomer.
Belzarena 2006	(-)	Sulfate		Belzarena SD indicated via email that he used a product by (b) (4). A web document containing drug information indicates that (b) (4) product (b) (4) contains "Ephedrine Sulfate (b) (4)". A web document from the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency) indicates that (b) (4) corresponds to CAS 299-42-3. The CAS Registry number 299-42-3 corresponds to (1R,2S)-(−)Ephedrine.
Bhattarai et al. 2010	(-)	HCl		Bhattarai B indicated via email that the ephedrine was from (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(−)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Dolci et al. 2011	(-)	HCl		Dolci M indicated that he most probably used Ephedrine HCl from (b) (4). He also indicated that the active principle corresponds by law to the Ph Eur, which describes the minus enantiomer only (1R, 2S). Dolci M also indicated he also may have used Ephedrine Bichsel at some point. A web document from SwissMedic confirms that both Ephedrine Bischsel and Ephedrine Streuli contained "Ephedrini hydrochloridum", which corresponds to the (-)enantiomer according to the Ph. Eur.
Ganeshanavar et al. 2011	(-)	HCl		Ganeshanavar A indicated via email that he used ephedrine hydrochloride manufactured by (b) (4) and that this product met the Indian Pharmacopia standards. (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(−)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.

Citation	Isomer (+/-)	Salt	Manufacturer	Contact History
Kansal et al. 2005	(-)	HCl	(b) (4)	Mohta M indicated via email that they used ephedrine hydrochloride from (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(−)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Kasaba et al. 2000	(-)	HCl	Unknown	(b) (4) (a pharmacist at (b) (4) Hospital) indicated that the hospital has used ephedrine in the form of (1R,2S)-2-Methylamino-1-phenylpropan-1-ol-monohydrochloride and that it has not changed since 1998.
Kitchen et al. 2014	(-)	HCl	(b) (4)	Kitchen CC indicated via email that the ephedrine used was from (b) (4) indicated that the products on the market (including (b) (4)) are made of the enantiomer (1R,2S)-2-(Methylamino)-1- phenylpropan-1-ol hydrochloride.
Lecoq et al. 2010	(-)	HCl		Lecoq JPH indicated via email that he used ephedrine hydrochloride from (b) (4). An email from (b) (4) indicated that the ephedrine hydrochloride is only "levogyre". Levorotary compounds are indicated with a (-) as a prefix, indicating that the product was the (-) enantiomer only.
Meersschaert et al. 2002	(-)	HCl	Unknown	Coriat P indicated via email that the ephedrine used in their study was comprised of only the levogyre isomer. He also indicated that the salt form was hydrochloride.
Meng et al. 2011a & Meng et al. 2011b	(-)	Sulfate	(b) (4)	(b) (4) confirmed via email that (b) (4) has been their primary wholesaler of ephedrine since prior to 2009 to the present. A label on DailyMed confirms that (b) (4) repackages product from (b) (4), which is ephedrine sulfate, USP, which indicates the (-) enantiomer only.
Nag 2010	(-)	HCl		This reference provides a picture of the box of ephedrine used in the study, which was identified as (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)- (−)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.
Ngan Kee et al. 2001 Ngan Kee et al. 2008b	(-)	Sulfate		Ngan Kee WD indicated via email that he used ephedrine sulfate from (b) (4) in all studies. (b) (4) indicated via email that the product is (-)ephedrine.
Nissen et al. 2010	(-)	HCl		Secher NH identified an ephedrine hydrochloride product from (b) (4) as the product used in the study. (b) (4) indicated that the products on the market (including (b) (4)) are made of the enantiomer (1R,2S)-2- (Methylamino)-1-phenylpropan-1-ol hydrochloride.
Pennekamp et al. 2011	(-)	HCl		(b) (4) indicated via email that they used ephedrine hydrochloride from (b) (4). A web document from the CBG Medicines Data Bank shows that the ephedrine is the (-)enantiomer.

Citation	Isomer (+/-)	Salt	Manufacturer	Contact History
Prakash et al. 2010	(-)	HCl	(b) (4)	Prakash S indicated via email that they used ephedrine hydrochloride from (b) (4) indicated that the CAS number of the API is 50-98-6. The CAS Registry number 50-98-6 corresponds to (1R,2S)-(−)Ephedrine Hydrochloride. The employee also writes that the ephedrine hydrochloride follows the Indian Pharmacopeia, which specifies the (-)isomer.

The review team evaluated this information and determined for which publications the Applicant had obtained adequate information to support the position that the negative isomer of ephedrine had been used in the clinical trial described in the publication and, therefore, considered to be supportive of the NDA. These publications are further discussed in Section 7 of this review.

Outstanding or Unresolved Issues

I agree with the review team that there are no product quality issues that would preclude approval of this application. The Applicant submitted adequate information to support an expiry of 24 months, when the product is stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any nonclinical pharmacology or toxicology studies in support of this NDA. The review team's assessment of the available published information, particularly regarding genotoxicity, carcinogenicity, and reproductive toxicology is summarized below (reproduced from Dr. Delatte's review).

> There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application. In several meetings with the Applicant prior to submission of the NDA, the Division communicated multiple issues to the Applicant. Firstly, as ephedrine possesses two chiral centers and exists as four stereoisomers, the Applicant was directed to identify the isomer utilized in all relied upon publications for safety and efficacy of (-)-ephedrine. Secondly, it was conveyed that if there is adequate clinical experience with the drug product, no general toxicology studies would be required to support an NDA. Thirdly, if the referenced nonclinical genetic toxicology and reproductive and developmental toxicology literature do not support labeling for the drug product, these studies would be required post-approval.
>
> The final drug product is ephedrine sulfate in water and therefore there are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants have been adequately qualified for safety. The rubber stopper is used in a marketed FDA-approved aqueous product and therefore the safety of the container closure system consisting of the glass vial and (b) (4) rubber stopper has been adequately qualified for safety.
>
> The nonclinical findings used to support the safety of the ephedrine sulfate product are briefly discussed below. Extensive clinical experience with this drug substance and literature support the local and systemic safety of ephedrine. Published acute

toxicology studies demonstrated that intravenous ephedrine caused mortality (at least 7-times the maximum recommended human dose (based on body surface area comparisons) but was generally preceded by a variety of clinical signs, including convulsions, uncoordination, and increased respiration (Chen, 1926b; Graham and Kuizenga, 1948; Marvola, 1976; Warren and Werner, 1946). In repeat-dose toxicity studies conducted in rats and mice, ephedrine was demonstrated to decrease body weight and food consumption in the absence of treatment-related findings following dietary administration for up to 2 years. There was no evidence of test article related adverse findings in mice orally administered up to approximately 29 mg/kg (2.4-times the maximum recommended dose of 50 mg based on body surface area comparisons) and rats orally administered up to approximately 11 mg/kg (1.8-times the maximum recommended dose of 50 mg based on body surface area comparisons).

In in vitro genetic toxicology studies evaluating ephedrine, negative results were obtained in the in vitro bacterial reverse mutation assay (Ames assay), in vitro chromosome aberrations assay, or the in vitro sister-chromatid exchange (SCE) assay. However, the genotoxic potential of ephedrine sulfate has not been evaluated in an in vivo genotoxicity assay. It is recommended that an in vivo genotoxicity assay is conducted with ephedrine sulfate as a post-marketing requirement. There was no evidence of carcinogenicity at dietary doses of up to 11 mg/kg/day in rats (approximately 2-times the maximum recommended daily dose of 50 mg/day) and 29 mg/kg/day in mice (approximately 3-times the maximum recommended daily dose of 50 mg/day).

The Applicant submitted an (b) (4) Overall, these reproductive toxicology studies were not deemed adequate to fulfill the requirements of an NDA and therefore it is recommended that ephedrine sulfate is evaluated in the standard battery of reproductive toxicology studies.

Taken together, the Applicant did not submit any new nonclinical studies to support this marketing NDA as none were required. The Applicant has provided adequate data to support the safety of the drug product substance and drug product specifications. However, several post-marketing requirements (PMRs) will be issued, which include four reproductive toxicology studies and one in vivo genetic toxicology study.

Outstanding or Unresolved Issues

I agree with the review team that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this application, and that the additional nonclinical information can be obtained through the following post-marketing study requirements:

1. A fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.
2. An embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.
3. An embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.
4. A pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.
5. An in vivo micronucleus assay with ephedrine sulfate.

5. Clinical Pharmacology/Biopharmaceutics

General Considerations

The Applicant did not conduct any clinical pharmacology studies. All the information regarding the clinical pharmacology of their product was derived from published literature. Dr. Nallani noted in his review that the most of the publications in the Applicant's submission do not contain adequate analytical information, such as QCs, recovery, stability, validations, etc. However, Dr. Nallani notes that there is information that appears to be consistent across different publications, i.e., the information available is qualitative rather than quantitative.

Pharmacokinetic Information

The pharmacokinetic characteristics of the (-) isomer of ephedrine are described by Dr. Nallani as follows (reproduced from his review):

> Since the proposed drug product is administered as an intravenous injection into the systemic circulation the bioavailability is 100% and it is considered self-evident. In addition, the other intravenous products, albeit marketed unapproved, described in publications used to support this NDA are simple solutions, there is no expectation of different bioavailability across these IV ephedrine solutions. Some of the publications used oral route, which can be used to support the qualitative characteristics independent of administration route, such as metabolism, excretion, etc. **Distribution:** Protein binding or volume of distribution following IV administration of (-)-ephedrine are unavailable. Publications of oral ephedrine pharmacokinetics suggest that the volume of distribution has been reported to range from 181 to 219 L (White et al. 1997, Gurley et al. 1998, Csajka et al. 2005).
>
> **Elimination:** Most of the publications from 1960's and 70's utilized analytical methods that do not adequately describe analytical validation. Although the most recent publications described analytical methodology adequately, they mainly describe oral (-)-ephedrine pharmacokinetics. Some of the excerpts of the publications that support qualitative statement on metabolism are described below. Taken together, observations generally support some metabolism of ephedrine and renal excretion to primary pathway of elimination. Csajka and colleagues (2005) also reported that orally administered (-)-ephedrine has an elimination half-life of about 6 hours and this could be similar if ephedrine were administered IV bolus.
>
> **Metabolism:** Extent and specific pathways of metabolism of (-)-ephedrine are unknown. However, based on latest published data following oral administration of (-)-ephedrine, it appears that norephedrine is formed due to N-demethylation.
>
> Sever and colleagues (1975) evaluated the metabolism of orally administered (-)[14C]ephedrine in 3 healthy, male, adult volunteers. Each subject received (-)[14C]ephedrine hydrochloride (approximately 30 mg). Urine was collected daily and the pH of the 24-hour urine samples was recorded. No attempt was made to regulate the pH of excreted urine. In the first 24 hours, 84% to 91% of the dose was excreted in urine, and 96% to 98% was excreted within 48 hours. The majority of excreted ephedrine consisted of unchanged (-)ephedrine (53%-74%) and norephedrine (8%-20%). Oxidative deamination occurred to a variable extent (4%-13%), resulting in the excretion of hippuric acid, benzoic acid, and 1,2-dihydroxy-1-phenylpropane. Other possible products of deamination were not detected. The pH values of the 24-hour urine collections for each subject showed little variation and were between 6.5 and 6.8; therefore, the variation found in the extent of excretion of metabolites could not be attributed to pH differences. The conclusions from authors are based on data from a limited number of subjects.

> Beckett and Wilkinson (1965a) reported that demethylation of (-)ephedrine was not a major pathway of metabolism in humans, with 79.3% of an oral dose being recovered in the urine in 24 hours as unchanged ephedrine and only 4.3% as norephedrine. Wilkinson and Beckett (1968a) followed up to their earlier study by examining the effect of urinary pH and route of administration on the metabolism of (-)-ephedrine. The authors concluded that the metabolism of (-)-ephedrine is pH-dependent, and the amount of (-)ephedrine excreted as norephedrine is increased approximately 2- to 5-fold from acidic to alkaline urine (Wilkinson and Beckett 1968a). Additionally, it was found that the route of administration (IV versus oral) does not influence the kinetics of elimination of ephedrine from the body. However, this publication describes data from few subjects without adequately describing the actual product ((-) or (+)-ephedrine) used in the study. Csajka and colleagues (2005) also reported that orally administered (-)-ephedrine is mostly excreted unchanged in the urine but is also metabolized to norephedrine to a small and variable extent, involving enzymatic N-demethylation and oxidative deamination of the side chain. The variance in affinity constant was relatively large, indicating substantial variation in the extent of metabolism of (-)-ephedrine to norephedrine. However, this pathway is minor compared with the renal elimination of oral (-)-ephedrine and, even after repeated drug intake, significant drug accumulation would not be expected.
>
> **Excretion:** Studies indicates that following oral administration of (-)-ephedrine may be mainly eliminated in the urine. Limited data following IV administration also suggest renal excretion of ephedrine in urine (See Beckett and Wilkinson 1965a description above).
>
> A single-dose, crossover study to evaluate oral absorption of commercial ephedrine sulfate USP (25 mg capsule) with oral solution NF XII (25 mg syrup) was conducted in 3 healthy male volunteers (Welling et al. 1971). Subjects were fasted overnight, doses were administered in the morning, and then subjects were fasted for 4 hours after dosing. Urine collections occurred over a 48-hour period. Urinary pH was not controlled, but urinary flow rates were maintained by regular water intake. Approximately 70% to 80% of ephedrine was excreted unchanged in the urine. The average overall mean elimination half-life of ephedrine was 5.99 hours at a mean urinary pH = 6.3.

Pharmacodynamic Information

Dr. Nallani notes the following in his review:

> Following IV administration of (–)-ephedrine, mean arterial pressure (MAP) increased from the pretreatment level of ≈50 mm Hg to the highest level of ≈80 mm Hg within 2 min after ephedrine administration (Meng L. et. al. 2011a). Dose-related increase in systolic blood pressure and heart-rate have been reported following IV administration of(–)-ephedrine by Ngan Kee et. al. (2000).

Special Populations

There were no publications submitted that described the pharmacokinetics in elderly, patients with renal or hepatic impairment, or pharmacokinetic differences between patients of different race or gender.

With respect to dosing of ephedrine in patients with renal impairment, Dr. Nallani noted that, based on a limited amount of urinary excretion data from publications over the past 40 years, there is qualitative information to indicate that ephedrine is mainly eliminated in the urine. Therefore, there is the expectation that renal disease is likely to impair ephedrine's elimination and result in a corresponding increase in elimination half-life. Subsequently, multiple

administrations of ephedrine in the setting of renal insufficiency could potentially result in toxic effects. However, Dr. Nallani also notes, that, due to the possible accumulation of ephedrine, the dose requirement in patients with renal impairment may be lower.

Because elderly patients are more likely to have decreased renal function, and ephedrine appears to be substantially excreted by the kidney, the risk of adverse reactions in this patient population would be greater.

There are data that indicate that ephedrine crosses the placenta. The potential clinical implications are discussed below in Section 10: Pediatrics.

With respect to the pediatric population, Dr. Nallani noted the following in his review.

> Given the fact that pharmacokinetic data is limited in adults following use of IV ephedrine, it is difficult to recommend a dosing regimen in pediatric patients based on pharmacokinetic principles. Therefore, a dose-response study evaluating different doses of ephedrine should be conducted with appropriate safety, PK and pharmacodynamic assessments in the ≥10 – 17 year age patients. Including adult patients in such a study will help resolve the lack of pharmacokinetic data and potentially help with understanding the dose-response similarity or lack thereof between adults and pediatrics.

Thorough QT Study

The review of post-marketing adverse event reports by the Division of Pharmacovigilance II did not identify a signal. Given the extensive history of clinical use, the team concluded that further assessment was not necessary.

Drug-drug Interactions

The Applicant did not conduct any studies to evaluate the impact of drug-drug interactions. However, Dr. Nallani noted that a limited number of publications that supported some information in specific populations.

Outstanding or Unresolved Issues

Although the Applicant did not conduct any clinical pharmacology studies and the majority of the publications submitted in support of the NDA did not contain all of the information that is usually included in a drug product's package insert, Dr. Nallani's final conclusion was that there was sufficient data to regarding the clinical pharmacology of ephedrine to support approval.

I agree with the review team's assessment that the Applicant be required to conduct a post-marketing study to evaluate the safety and pharmacodynamics/pharmacokinetics of ephedrine in patients between the ages of 12 and 16 years. I also agree with the review team that there are no clinical pharmacology issues that would preclude approval of this application.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The Applicant did not conduct any clinical trials in support of the efficacy of ephedrine. Instead, the Applicant submitted the results from several publications from the medical literature. As noted above, the Applicant had been advised in the meetings that transpired prior to the NDA submission that, in order for an article to be deemed supportive of that application, it was imperative that the isomeric identity of the ephedrine used in the clinical trial described in the publication be established.

The Applicant identified 18 publications in which it was felt that enough information about the isomer was obtained to permit the publication to be used in support of the NDA. The review teams evaluated the information and determined that, for 15 of these publications, the Applicant had been able to research and establish sufficient information about the ephedrine isomer used in the clinical trial reported in the publication to have that publication deemed to be reliable enough to support the NDA. The following table, adapted from the Applicant's submission and Dr. Luckett's review, lists the publications and the number of subjects that received ephedrine in the trials reported in the publications.

Citation	Salt	Manufacturer	No. of subjects receiving ephedrine
Adigun et al. 2010	HCl	(b) (4)	31
Belzarena 2006	Sulfate		38
Bhattarai et al. 2010	HCl		30
Ganeshanavar et al. 2011	HCl		30
Kansal et al. 2005	HCl		30
Kitchen et al. 2014	HCl		9
Lecoq et al. 2010	HCl		21
Meng et al. 2011a	Sulfate		29
Meng et al. 2011b			
Nag 2010	HCl		50
Ngan Kee et al. 2001	Sulfate		23
Ngan Kee et al. 2008	Sulfate		74
Nissen et al. 2010	HCl		12
Pennekamp et al. 2011	HCl		7
Prakash et al. 2010	HCl		30
Total No. of subjects			414

These publications reported the results of intravenous ephedrine being used to treat hypotension in three different clinical scenarios:

1. Randomized, double-blind, positive control in women having cesarean section with spinal anesthesia
2. Randomized, double-blind, positive control in patients having surgeries (other than cesarean section) with spinal anesthesia
3. Positive control trial in patients having surgery with general anesthesia

Additional information regarding these publications is summarized in the table on the following page, adapted from Dr. Luckett's review and the Applicant's submission.

Literature Citation (Study Site Location; Dates of Study Conduct)	Efficacy Endpoint(s)	Hypotension Threshold Used for Initiation of Treatment	Treatment Groups (n)	Dose/ Regimen	Post-Pressor Blood Pressure Changes	
					Magnitude (mean mmHg values±SD)	Time Course
Women Undergoing C-Section Delivery Under Spinal Anesthesia						
Adigun et al. 2010 (Nigeria; Jul – Dec2005) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Restoration of systolic blood pressure (SBP) ≥ 70% of baseline value	Decrease in systolic blood pressure (SBP) ≥ 30% or < 100 mmHg	Eph (7)	Single 5 mg {4.1 mg FB} IV bolus	Increase in SBP above hypotension threshold reached by all patients	Reported graphically only
			Phe (8)	Single 100 µg IV bolus	Increase in SBP above hypotension threshold reached by all patients	Reported graphically only
Belzarena 2006 (Brazil; dates not stated) (-)Ephedrine Sulfate = Eph Etilefrine = Eti	Restoration of blood pressure to within 20 mmHg of SBP or MBP	Decrease in systolic blood pressure (SBP) or mean blood pressure ≥ 20 mmHg	Eph (38)	10 mg {7.7 mg FB} IV bolus 22 (58%) received single bolus	Increase in SBP above hypotension threshold reached by all patients	Not reported
			Eti (41)	2 mg IV bolus 27 (66%) received single bolus	Increase in SBP above hypotension threshold reached by all patients	Not reported
Bhattarai et al. 2010 (India; May 2007 – May 2008) (-)Ephedrine HCl = Eph Phenylephrine = Phe Mephentermine = Mep	Restoration of systolic blood pressure (SBP) ≥ 80% of baseline value	Decrease in systolic blood pressure (SBP) ≥ 20% or < 90 mmHg	Eph (30)	5 mg {4.1 mg FB} IV bolus Mean ± SD number of bolus doses = 2.5 ± 0.5	Baseline SBP = 116.9±6.6 Increase in SBP above hypotension threshold reached by all patients Maximum mean SBP after Eph = 111.7±9 3	SBP post- Eph approached baseline values by 15 min
			Phe (30)	25 µg IV bolus Mean ± SD number of bolus doses = 3.5 ± 0.5	Baseline SBP = 116 5± 5.4 Increase in SBP above hypotension threshold reached by all patients Maximum mean SBP after Phe = 117.7±5.8	SBP post-Phe approached baseline values by 12 min
			Mep (30)	6 mg IV bolus Mean ± SD number of bolus doses = 2.9 ± 0.4	Baseline SBP = 114 2± 19.6 Increase in SBP above hypotension threshold reached by all patients Maximum mean SBP after Mep = 113.4± 7 9	SBP post-Mep approached baseline values by 30 min
Ganeshanavar et al. 2011 (India; Nov 2010 – Aug 2011) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Restoration of systolic blood pressure (SBP) ≥ 80% of baseline value	Decrease in systolic blood pressure (SBP) ≥ 20% or < 90 mmHg	Eph (30)	6 mg {4.9 mg FB} IV bolus # bolus, (patient %) Single, 57% Two, 27% Three, 16% Mean ± SD total dose = 9.6 (4.6) mg {7.8 (3.7) mg FB}	Baseline SBP = 124.2±5.9 Increase SBP above hypotension threshold reached by all patients Maximum mean increase in SBP after Eph = 33.1	Approx 80% of increase in SBP post-Eph by 8 min

Mephentermine = Mep			Phe (30)	100 µg IV bolus # bolus, (patient %) Single, 77% Two, 17% Three, 6% Mean ± SD total dose = 130 (50) µg	Baseline SBP = 123 5±5.0 Increase in SPB above hypotension threshold reached by all patients Maximum mean increase in SBP after Phe = 33.5	Approx 80% of increase in SBP post-Phe by 6 min
			Mep (30)	6 mg IV bolus # bolus, (patient %) Single, 47% Two, 43% Three, 10% Mean ± SD total dose = 9.8 (4.0) mg	Baseline SBP = 121 1±6.8 Increase in SBP above hypotension threshold reached by all patients Maximum mean increase in SBP after Mep = 33.1	Approx 80% of increase in SBP post-Mep by 8 min
Kansal et al. 2005 (India; dates not stated) (-)Ephedrine HCl = Eph Mephentermine = Mep	Restoration of blood pressure ≥ 80% of baseline value	Decrease in systolic blood pressure (SBP) ≥ 20% or < 100 mmHg	Eph (30)	Initial 5 mg {4.1 mg FB} IV bolus dose then 2.5 mg/min {2.1 mg/min FB} and increased by 0.5 mg/min {0.41 mg/min FB} for every further 10% decrease in SBP and infusion stopped if SBP increased above baseline values Total mean ± SD dose of Eph = 19.9 ± 11.5 mg {16.3 ± 9.4 mg FB}	Baseline SBP = 122.5± 8.3 Hypotension Threshold = 101.7± 2.8 Increase in SBP above hypotension threshold reached by all patients	Reported graphically only
			Mep (30)	Initial 5 mg IV bolus dose then 2.5 mg/min and increased by 0 5 mg/min for every further 10% decrease in SBP and infusion stopped if SBP increased above baseline values Total mean ± SD dose of Mep = 17.2 ± 10.4 mg	Baseline SBP = 121 5± 10.0 Hypotension Threshold = 102.2± 3.5 Increase in SBP above hypotension threshold reached by all patients	Reported graphically only
Ngan Kee et al. 2001 (China [Hong Kong]; dates not stated) (-)Ephedrine Sulfate = Eph Metaraminol = Met	Restoration of SAP to ≥ 90% of baseline value	Decrease in systolic arterial pressure (SAP) > 10%	Eph (25 but only 23 dosed)	Initial 10 mg {7.7 mg FB} IV bolus dose then 5 mg/min {3.9 mg/min FB} and stopped when SAP increased above baseline values Total mean ± SD dose of Eph = 50.0 ± 25.1 mg {38.5 ± 19.3 mg FB}	All patients achieved efficacy endpoint Mean baseline SAP not reported Lowest recorded mean ±SD SAP = 96± 13 (range74 – 118) Highest recorded mean ±SD SAP = 137± 16 (range 117 – 174)	Reported graphically only
			Met (25 but treatment data from only 23 available)	Initial 0.5 mg IV bolus dose then 0.25 mg/min and stopped when SAP increased above baseline values	All patients achieved efficacy endpoint Mean baseline SAP not reported	Reported graphically only

				Total mean ± SD dose of Met = 3.1± 0.9 mg	Lowest recorded mean ±SD SAP = 92± 16 (range 58 – 120) Highest recorded mean ±SD SAP = 138± 16 (range 115 – 171)	
Ngan Kee et al. 2008b (China [Hong Kong]; dates not stated but enrollment occurred over 2 years) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	Restoration of SBP to ≥ 100 mm Hg	SBP < 100 mmHg	Eph (74)	10 mg {7.7 mg FB} IV bolus with the following dose frequency distribution: 1 = 21 pts 2 = 23 pts 3 = 16 pts 4 = 6 pts 5 = 5 pts >5 = 2 pts	Baseline SBP not reported Minimum median (inter quartile range) SBP = 95 (88 – 102) Maximum median (inter quartile range) SBP = 127 (120 – 138)	Not reported
			Phe (74)	100 µg IV bolus with the following dose frequency distribution: 1 = 24 pts 2 = 13 pts 3 = 12 pts 4 = 10 pts 5 = 5 pts >5 = 10 pts	Baseline SBP not reported Minimum median (inter quartile range) SBP = 96 (89 – 101) Maximum median (inter quartile range) SBP = 127 (120 – 135)	Not reported
Nag 2010 (India; Dec 2007 – Dec 2008) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Restoration of systolic blood pressure (SBP) ≥ 80% of baseline Value	Decrease in systolic blood pressure (SBP) ≥ 20% or < 90 mmHg	Eph (50)	6 mg {4.9 mg FB} IV bolus whenever SBP dropped below pre-specified threshold Mean ± SD number of Doses = 1.4 ± 0.6 (range 1 – 3) Mean Total Dose = 8.4 mg {6.9 mg FB}	Baseline SBP = 123.1±9.0 Hypotension Threshold = 82.1±12.8 Maximum SBP after Eph = 109.8±7.3 (18 min)	SBP restored to ≥80% of baseline value at 10 min (after only or last bolus dose)
			Phe (50)	40 µg IV bolus whenever SBP dropped below pre-specified threshold Mean ± SD number of Doses = 1.2 ± 0.5 (range 1 – 3) Mean Total Dose = 48 µg	Baseline SBP = 123 5±7.8 Hypotension Threshold = 83.6±7 9 Maximum SBP after Phe = 116.3±10.9 (6 min)	SBP restored to ≥80% of baseline value at 2 min (after only or last bolus dose)
Prakash et al. 2010 (India; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine =Phe	Restoration of systolic blood pressure (SBP) ≥ 80% of baseline value	Decrease in systolic blood pressure (SBP) ≥ 20%	Eph (30)	6 mg {4.9 mg FB} IV bolus whenever SBP dropped below pre-specified threshold Mean Number of Doses = 2 (range 1 – 4)	Baseline SBP = 128±8 Hypotension Threshold = 100 (range 80 -112) Maximum SBP after Eph = 122 (range 110 – 140)	Reported graphically only

				Mean ± SD Total Dose = 12.5 ± 5.1 mg {10.3 ± 4.2 mg FB}		
			Phe (30)	100 µg IV bolus whenever SBP dropped below pre-specified threshold Mean Number of Doses = 2 (range 1 – 3) Mean ± SD Total Dose = 160 ± 60 µg	Baseline SBP = 126±9 Hypotension Threshold = 93 (range 70 – 110) Maximum SBP after Phe = 127 (range 100 – 150)	Reported graphically only
Patients Undergoing Other Surgeries (Non-C-Section Delivery)Under Spinal Anesthesia						
Lecoq et al. 2010 (Belgium; dates not stated) (-)Ephedrine HCl = Eph Norepinephrine = Nor	Restoration of MAP to ≥90% of baseline value	Decrease in mean arterial pressure (MAP) > 10% (after stabilization to approx. 10% below baseline levels with supplementary fluid loading)	Eph(21)	Maximum of 10 mg {8.2 mg FB} IV bolus (0.2 mg/kg) {0.16 mg FB}, single Mean ± SD dose = 9.7± 0.3 mg {8.0 ± 0. 25mg FB}	Baseline MAP = 93± 10 MAP Hypotension Threshold = 83± 8 Post-Eph MAP = 95 ± 8	Not reported
			Nor (23)	Infusion 0.1 mg/mL at a rate of 3 mL/h stopped when MAP returned to baseline Mean ± SD total dose = 0.88 ± 0.56 µg/kg	Baseline MAP = 93± 9 MAP Hypotension Threshold = 83± 7 Post-Nor MAP = 92± 9	Not reported
Patients Undergoing Surgery Under General Anesthesia						
Kitchen et al. 2014 (Denmark; dates not reported) (-)Ephedrine HCl = Eph Adrenaline = Adr Phenylephrine = Phe Noradrenaline = Norad Calcium chloride = Cal	Increase in MAP above 60 mmHg	Decrease in MAP to < 60 mmHg	Eph (9)	10 mg {8.2 mg FB} IV bolus	Hypotensive threshold MAP = 55 ± 3 Post-Eph MAP = 74 ± 9	Not reported
			Adr (6)	1 -2 µg IV bolus	Hypotensive threshold MAP = 53 ± 3 Post-Adr MAP = 72 ± 11	
			Phe (11)	100 – 200 µg IV bolus	Hypotensive threshold MAP = 51 ± 5 Post-Phe MAP = 78 ± 9	
			Norad (11)	2 – 4 µg IV bolus	Hypotensive threshold MAP = 53 ± 5 Post-Norad MAP = 72 ± 12	
			Cal (10)	5 mmol IV bolus	Hypotensive threshold MAP = 49 ± 7 Post-Cal MAP = 57 ± 16	
Meng et al. 2011a and Meng et al. 2011b	Increase in MAP ≥80% of	Decrease in mean arterial pressure	Eph (29) Note: 1	5 – 20 mg {3.85 – 15.4 mg FB} IV bolus (single)	Baseline MAP not stated Hypotensive threshold MAP =	Example presented graphically

(US; dates not stated) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	baseline value or above 60 mmHg	(MAP) > 20% or a MAP to < 60 mmHg	additional patient received Eph only but not included in reported analysis		53 ± 12 Post-Eph MAP = 80 ± 13	Peak MAP effect within 2 min of Eph bolus
			Phe (29)	100 – 200 µg IV bolus (single)	Baseline MAP not stated Hypotensive threshold MAP = 60 ± 10 Post-Phe MAP = 97 ± 15	Example presented graphically Peak MAP effect within 2 min of Phe bolus
Nissen et al. 2010 (Denmark; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Increase in MAP above 60 mmHg	Decrease in MAP to < 60 mmHg	Eph (12)	10 mg {8.2 mg FB} IV bolus	Baseline MAP = 91 ±18 Hypotensive threshold MAP = 53 ± 9 Post-Eph MAP = 79 ± 8	Presented graphically Meant (range) time to achieve highest MAP = 83 (21 – 134) sec
			Phe (13)	100 µg IV bolus	Baseline MAP = 90 ±19 Hypotensive threshold MAP = 51 ± 12 Post-Phe = 81 ± 13	Presented graphically Meant (range) time to achieve highest MAP = 41 (30 - 83) sec
Pennekamp et al. 2011 (Netherlands; Feb 2009 – Jun 2011) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Increase MAP to ≥80% of baseline value	Decrease in mean arterial pressure (MAP) > 20%	Eph (7)	5 – 10 mg {4.1 – 8.2 mg FB}IV bolus	Baseline MAP not reported Hypotensive threshold MAP = 79 ± 12 3 minutes post-Eph MAP = 89 ± 11	Presented graphically
			Phe (4)	50 – 100 µg IV bolus	Baseline MAP not reported Hypotensive MAP = 84 ± 6 3 minutes post-Phe MAP = 102 ± 6	Presented graphically

Note:

- FB = Free base
- For the dose/regimen column for the Belzarena/ephedrine row: 22 of 38 subjects who became hypotensive requiring ephedrine had correction of the hypotension with the first dose of ephedrine.
- For Ngan Kee, el al., 2008: Values in the "Magnitude" column for the ephedrine treatment group represent the median interquartile range minimum recorded systolic blood pressure (95) for the ephedrine treatment group (n= 102) and median interquartile range maximum recorded systolic blood pressure (127) for the ephedrine treatment group (n= 102). 102 subjects were randomized to the ephedrine treatment group, but only 74 subjects required ephedrine.

Based on the information contained in the above publications, as well as in the rest of the NDA submission, the review team was able to conclude that substantial evidence supporting the effectiveness of ephedrine and the dosing regimen proposed by the Applicant had been provided. Dr. Luckett noted the following in her review:

> Overall, clinical trials in the publications submitted to support the efficacy of Akovaz demonstrated ephedrine's ability to increase blood pressure. Most of the subjects in the clinical trials in the submitted publications who received ephedrine were female parturients undergoing spinal. It is acceptable to extrapolate efficacy to the rest of the population undergoing anesthesia because, in the publications provided to support efficacy, ephedrine's ability to increase blood pressure did not appear markedly different in those receiving general anesthesia compared to neuraxial anesthesia and also did not appear to vary substantially based on type of surgical procedure. (Source: NDA 208089 page 52 of Integrated Summary of Efficacy)
>
> The proposed dosing for Akovaz is 5 mg to 10 mg intravenous bolus. This is the most common dose recommendation in the table of authoritative texts (section 6.1.8 of this review) and is consistent with the ephedrine bolus dosing in the publications submitted to support efficacy.

Outstanding or Unresolved Issues

I agree with the review team that there are no efficacy issues identified that would preclude approval of this application.

8. Safety

As noted in Dr. Luckett's review the safety database submitted by the Applicant was entirely derived from the published literature. The Applicant submitted a total of 56 publications to support the safety of ephedrine, which were designated as either "primary" or "supplementary." These publications were divided into the following categories.

a) Primary publications intended to support efficacy and safety
b) Primary publications intended to support safety
c) Supplementary publications where ephedrine was used to treat hypotension, enantiomeric structure not confirmed
d) Supplementary publications where ephedrine was used to prevent hypotension, enantiomeric structure confirmed

In discussions with the Applicant prior to the submission of the NDA it had been noted that, ideally, publications which reported the use of the negative isomer of ephedrine to treat hypotension would be best, but that publications where it was not clear as to what isomer of ephedrine was used in the clinical trial would still be considered useful. This was because, contrary to the effectiveness, the safety profile of the ephedrine would not be as markedly affected by the specific isomeric structure. In addition, publications that reported the use of ephedrine for the prevention of hypotension would also be considered useful.

The following table, adapted from Dr. Luckett's review, summarizes the information about the number of subjects and ephedrine exposure that constitutes the safety database.

Type of study		Treatment	Treatment	Treatment	Prevention	Treatment
Did the applicant attempt to confirm that the formulation in the publication is (-)-ephedrine (Y/N)		Yes	Yes	Yes	Yes	No
Type of anesthesia		Spinal	Spinal	General anesthesia with or without epidural	Spinal or general anesthesia	Spinal or epidural with or without general anesthesia
Patient population		cesarean section	Surgery (not cesarean section)	Surgery (not cesarean section)	cesarean section or other surgery	cesarean section or other surgery
IV bolus dose range: mg		3-10	7.5-10	3-20	5-30	5-30
Range of total # of boluses		1-5[a]	≥1	≥1	0-3	0-8
Infusion concentration range		n/a	n/a	n/a	0.03- 8mg/mL	n/a
Mean (± SD) total dose range	Min (mg)	1.7 ± 17	7.5	Not reported	5.0 ± 1.1	4.9 ± 1.0
	Max (mg)	50 ± 25.1	9.7 ± 0.3	Not reported	55 ± 11.7	41 ±4
# of patients receiving ephedrine		477[b]	31	87	662[c]	616[d]

[a] Two subjects in Ngan Kee et al. 2008b were reported to have received "greater than 5" boluses (Ngan Kee, Khaw, et al. 2008)
[b] Only subjects who received the first dose of ephedrine after becoming hypotensive are included; those receiving ephedrine to prevent hypotension are not included
[c] Only subjects given ephedrine for the prevention of hypotension (when normotensive) are included; subjects who did not receive ephedrine for the prevention of hypotension were not included
[d] Only subjects who received the first dose of ephedrine after becoming hypotensive are included; those receiving ephedrine to prevent hypotension are not included. Subjects in Berends et al. 2005 are not included because all subjects treated for hypotension with ephedrine already received ephedrine for prevention of hypotension

In the studies that were intended to support the safety of ephedrine for this indication, there were no deaths reported. One serious adverse event was reported, which involved the admission of a neonate to the neonatal intensive care unit because of feto-maternal transfusion syndrome.

Adverse Events Resulting in Discontinuation

As noted in Dr. Luckett's review, information about discontinuations due to adverse events was not provided in most of the publications.

Common Adverse Events

The safety findings reported in the publications were evaluated based on whether the publications were reporting on treatment of hypotension or prevention of hypotension, and whether the Applicant had been able to confirm whether the isomeric structure of the ephedrine used in the clinical trial had been confirmed. The adverse events most commonly reported in the publications are summarized in the table below, adapted from Dr. Luckett's review.

	(-)Ephedrine Confirmed, Treatment, N=258 n (%)	(-)Ephedrine Confirmed, Prevention, N=407 n (%)	Ephedrine Isomer Unconfirmed, Treatment, N=296 n (%)	Total N=961 n (%)
Nausea	36 (14%)	53 (13%)	45 (15%)	134 (14%)
Vomiting	12 (5%)	32 (8%)	14 (5%)	58 (6%)
Nausea and/or Vomiting	32 (12%)	55 (14%)	45 (15%)	132 (14%)
Tachycardia	13 (5%)		8 (3%)	21 (2%)
Bradycardia	1 (0.4%)		7 (2%)	8 (1%)
Reactive Hypertension	3 (1%)	103 (25%)		122 (13%)
Thumping heart	3 (1%)			3 (0.3%)
Shivering		5 (1%)		5 (0.5%)
R-R Variability	1 (0.4%)			1 (0.1%)
Ventricular ectopics	1 (0.4%)			1 (0.1%)
Dizziness	1 (0.4%)			1 (0.1%)
Restlessness	1 (0.4%)			1 (0.1%)
TOTAL	258	407	296	96

Evaluation of FDA's Adverse Event Reporting System (FAERS) Database

The Division of Pharmacovigilance II in the Office of Surveillance and Epidemiology conducted a review of the case reports in the FAERs database and a review of the published medical literature. This was done in order to provide an overview of potential new signals that should be incorporated into the package insert.

The search of the FAERS database covered the time period from 1969 to January 20, 2016. The literature search consisted of a search of PubMed for human case reports over the last 5 years, and the specific search terms were: "ephedrine," "heart," "cardiac," "stroke," "adverse," and "safety."

The results of the search are described below, reproduced from the review:

> The search of the FAERS database retrieved a total of 288 reports (including duplicates). Though there were 29 reports coded with a fatal outcome, after deduplication and excluding cases that were not relevant, there were 11 unique cases describing a fatal outcome with ephedrine injection use. Analysis of these reports did not find any report of death causally linked to the ephedrine injection alone. The most common use for ephedrine injection is severe hypotension. Since cardiovascular adverse events are associated with the use scenarios for ephedrine, DPV expected FAERS reports of ephedrine to be associated with adverse cardiovascular outcomes even if the drug was not a cause of these outcomes.
>
> A search of the recent medical literature identifies no evidence of stroke or cardiac events resulting from ephedrine injection. It does identify a number of publications describing that fetal acidosis is more likely to result from use of ephedrine during cesarean section compared with phenylephrine. Though it appears that this fact is well known in the

obstetric community (Nag, 2015) it could be useful to include information about the potential for neonatal acidosis in labels for ephedrine. The proposed Flamel label already includes information about the possible adverse event in sections 8 and 9.

The OSE review team's conclusion was that there were no new safety signals for ephedrine identified in FAERS or the published literature.

The OSE reviewers did not agree with the Applicant's proposal for Section (b) (4) of the package insert. Their rationale is noted below:

(b) (4)

Outstanding or Unresolved Issues

I agree with the review team that there are no safety issues identified that would preclude approval of this application.

9. Advisory Committee Meeting

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

10. Pediatrics

The Pediatric Review Committee (PeRC) met on March 9, 2016, to discuss the Applicant's proposed pediatric plan. The Applicant had requested a partial waiver for pediatric patients younger than (b) (4) years of age could be waived because they concluded that (b) (4) he drug is not likely to be used by a substantial number of pediatric patients in that age group." They requested a deferral for the studies in pediatric patients between the ages of (b) (4) and 16 years of age. The PeRC concurred with the Applicants request for partial waiver and deferral.

After additional internal discussions, it was decided that upper limit of the age group to be waived should be 12 years of age.

As noted above, Dr. Nallani noted that there is limited pharmacokinetic data in adults following intravenous administration of ephedrine; subsequently, it is difficult to recommend a dosing regimen in pediatric patients based on pharmacokinetic principles. Therefore, it would be necessary for the Applicant to conduct a dose-response study with appropriate safety, pharmacokinetic, and pharmacodynamic assessments in the pediatric patients.

The timeline for the deferred clinical pediatric studies is for the protocol to be submitted by May 2017, the study completed by May 2020, and the final study report to be submitted by May 2021.

In addition, in order to support the clinical trial in pediatric patients, the Applicant will be required to conduct a juvenile toxicity study in rats. The timeline for this nonclinical study is for the final study report to be submitted by November 2017.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Office of Professional Drug Promotion, and the Division of Medication Error Prevention and Analysis. Their recommendations were reviewed and incorporated in the appropriate places in the label.

OSI / Division of Good Clinical Practice Compliance (DGCPC) Audits

There were no clinical trials conducted by the Applicant, therefore, there was no need for audits to be conducted by the DGCPC.

Controlled Substances Staff Consultation

The Applicant was requested to conduct a review of the published literature and provide an overview of the abuse potential of the formulation. The Controlled Substances Staff (CSS) concurred with the Applicant that the product poses minimal risks for abuse and does not need to be scheduled under the Controlled Substances Act. The CSS also agreed that because the product will be used to treat hypotension in the setting of anesthesia, then its availability will be only be prescription, and used in a highly controlled setting.

The CSS consult did note, and it was previously conveyed to the Applicant, that the importation and manufacture of this product is subject to the controls imposed by the Combat Methamphetamine Epidemic Act of 2005, as List 1 chemical.

Financial Disclosure

The Applicant did not conduct any clinical trials in support of this application. The Applicant relied on published studies in the public domain. The Applicant included a table of the publications that utilized to support the efficacy of the ephedrine sulfate, and noted that they had not engaged in any financial arrangement with any of the investigators listed in the following table (reproduced from the Applicant's submission).

Title and Citation	Corresponding Author	Contact Information
Adigun et al. 2010	Dr. T.A. Adigun	(b) (6)
Belzarena 2006	Dr. Belzarena	
Bhattarai 2010	Dr. Bhattarai	
Dolci et al. 2011	Dr. Dolci	
Ganeshanavar et al. 2011	Dr. Ganeshanavar	
Kansal et al. 2005	M. Mohta	
Kasaba et al. 2000	Dr. Kasaba	
Kitchen et al. 2014	Dr. Kitchen	
Lecoq et al. 2010	Dr. Lecoq	
Meng et al. 2011a & Meng et al. 2011b	Dr. Cannesson	
Nag 2010	Dr. Nag	
Ngan Kee et al. 2001 & Ngan Kee et al. 2008b	Dr. Ngan Kee	
Nissen et al. 2010	Dr. Secher	
Meersschaert et al. 2002	Dr. Coriat	
Pennekamp et al. 2011	Dr. de Borst	
Prakash et al. 2010	Dr. Prakash	

Outstanding or Unresolved Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Modifications were made by the review team to all the sections of the proposed package insert.

As noted above, the Division of Pharmacovigilance II conducted a review of the FAERS database and the published medical literature in an attempt to identify any new safety signal that should be included in the package insert. They concluded that no new safety signal was identified, but did note that the Applicant's proposal for Section (b) (4) of the package insert (b) (4) should be deleted.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

I concur with the review team that the Applicant has submitted sufficient evidence to demonstrate the effectiveness and safety of the product for the treatment of

hypotension in the setting of anesthesia. As noted in Dr. Luckett's review, although ephedrine has been associated with a risk of hypertension and tachycardia, its use in the setting of perioperative hypotension has a favorable risk:benefit assessment in view of the increased morbidity and mortality associated with such hypotension in this clinical setting.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

As noted above, the Applicant will be required to conduct the following studies (with their respective timelines as noted):

3062-1 Conduct a juvenile toxicity study in rats to support treatment of children and adolescents with AKOVAZ (ephedrine sulfate) injection by IV administration.

Final Protocol Submission:	05/2016
Study Completion:	05/2017
Final Report Submission:	11/2017

3062-2 Conduct a single open-label study to evaluate the safety and pharmacodynamics/ pharmacokinetics of intravenous ephedrine dosed on a mg/kg basis with provisions for up-titration (dose or frequency) as clinically indicated in patents 12-16 years.

Final Protocol Submission:	05/2017
Study Completion:	05/2020
Final Report Submission:	05/2021

3062-3 Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.

Final Protocol Submission:	11/2016
Study Completion:	08/2017
Final Report Submission:	05/2018

3062-4 Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.

Final Protocol Submission:	11/2016
Study Completion:	05/2017
Final Report Submission:	03/2018

3062-5 Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.

Final Protocol Submission:	11/2016
Study Completion:	08/2017
Final Report Submission:	06/2018

3062-6 Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

Final Protocol Submission:	11/2016
Study Completion:	07/2018
Final Report Submission:	07/2019

3062-7 Conduct an in vivo micronucleus genotoxicity assay with ephedrine sulfate.

Study Completion:	07/2016
Final Report Submission:	01/2017

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
04/29/2016