CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208289Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208289 SDN 1, 15	Submission Date(s): 6/30/2015
Brand Name	Ephedrine Sulfate Injection
Generic Name	Ephedrine Sulfate Injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Flamel Ireland Limited
Relevant IND(s)	116266
Submission Type; Code	Original NDA; 505(b)(2)
Formulation; Strength(s)	Solution; 50 mg/mL.
Indication	Treatment of clinically important hypotension in the setting of anesthesia.
Proposed Dosage Regimen	The recommended dosages for the treatment of clinically important hypotension in the setting of anesthesia is an initial dose of 5 to 10 mg administered by intravenous bolus. May administer additional boluses as needed; not to exceed a total dosage of 50 mg.

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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a clinical pharmacology perspective provided that labeling changes are accepted by the sponsor.

1.2 Phase IV Commitments

As part of the pediatric assessment, a safety, PK, dose-response study must be conducted in pediatric patients ("(b) (4)-16 yrs) requiring ephedrine when experiencing hypotension due to anesthesia.

1.3 Summary of Clinical Pharmacology Findings

The NDA 208289 was submitted by Flamel Ireland Limited to market Ephedrine Sulfate Injection, USP which is the (–)-ephedrine isomer. The sponsor has not marketed the proposed product without Agency's approval; however, marketed unapproved formulations of ephedrine utilizing either the sulfate or hydrochloride salt exist in United States. The sponsor has submitted literature evidence to support the clinical indication of Ephedrine Sulfate Injection, USP for the treatment of clinically important hypotension in the setting of anesthesia. The sponsor contends that the evidence of Ephedrine Sulfate Injection, USP safety is considered relevant if the drug used in a published study was either the sulfate salt or hydrochloride salt of the (–)-ephedrine isomer.

The sponsor has not conducted any studies in support of this NDA. Ephedrine has been used in the United States for decades as marketed unapproved products. In support of the clinical pharmacology submission, the sponsor reviewed published literature and submitted supporting information. Prior to submission of the NDA the sponsor was informed of the need to identify the specific enantiomer (–)-ephedrine or (+)-ephedrine or racemate) and salt (HCl, sulfate, etc.) employed for a clinical pharmacology, clinical safety and efficacy investigation in a given publication. In addition, the sponsor was informed of the need to adequately identify the bioanalytical methodology and validation information as it relates to the FDA standards.

As such review of the submitted publications and the justification by the sponsor reveals that most of the publications submitted in the application do not have adequate analytical information (e.g., QCs, recovery, stability, validations, etc.). Based on the current clinical pharmacology standards, none of the publications are adequate and are not optimal in constructing the information for the Labeling purpose. In sponsor's words *"The majority of the published efficacy studies included in this NDA do not identify the manufacturer or the trade name of the ephedrine drug product used in the study. Through email exchanges with publication authors and drug manufacturers, the identity of the drug product used in many of the efficacy studies was ascertained."*

"The majority of the published safety and clinical pharmacology studies included in this NDA do not identify the manufacturer or the trade name of the ephedrine drug product used in the study. Tables(See section 2.6 Analytical) *provide the contact history and manufacturer, salt form, and isomer of the ephedrine product (if known) for the safety*

and clinical pharmacology papers with parenteral ephedrine administration in this NDA for papers with and without confirmed (-)ephedrine respectively."

However, it appears that the following information is consistent across different publication regardless which analytical methods used. In other words, the information available is mostly qualitative rather than quantitative. There are publications that the nonclinical and medical reviewer's found acceptable with regard to safety and efficacy endpoints. Based on available literature, the review team has decided that the effectiveness and safety of the proposed dosing regimen has been established. However, those publications are without adequate pharmacokinetic data. For example, Meng et. al. 2011a & b describe pharmacodynamics of cardiovascular effects of parenteral (–)-ephedrine without any information on pharmacokinetics of IV epherine.

Mechanism of Action: Ephedrine is a sympathomimetic agonist of both α- and β-adrenergic receptors. Ephedrine stimulates heart rate and increases cardiac output and variably increases peripheral resistance; as a result increases blood pressure.

Pharmacodynamics of IV (–)-ephedrine:

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).

Pharmacokinetics: As mentioned above ephedrine is marketed unapproved in the United States by different manufacturing companies. Although Flamel (or Eclat Pharmaceuticals) does not market an unapproved product, the proposed product seems to a simple sterile USP solution for IV injection as with other products. Current USP specification for ephedrine solution for injection requires use of (–)-ephedrine.

Table: Comparison of Flamel/Éclat's Proposed Formulation to Currently Manufactured Unapproved Parenteral Formulations (per mL)

Company	Ephedrine Salt	Quantity	Water for injection qs	Labeled as USP	pH Range	Marketed Unapproved
Flamel/Éclat Pharmaceuticals	Sulfate	50 mg	Yes	USP	4.5 to 7.0	No
(b) (4)	Sulfate	50 mg	Yes	USP	4.5 to 7.0	Yes
	Sulfate	50 mg	Yes	USP	4.5 to 7.0	Yes
	Sulfate	50 mg	Yes	USP	4.5 to 7.0	Yes
	Sulfate	50 mg	Yes	USP	Unknown	Yes

qs: sufficient quantity
Source: Table 3: Section 2.7.1 Summary of Biopharmaceutic Studies.

Chemistry reviewers Drs. Ciby Abraham and Julia Pinto have indicated that due to steric hindrance (-)-(1R,2S)–enantiomer of ephedrine cannot convert to (+)-(1R,2S)-enantiomer of ephedrine.

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.

Very limited PK data are available for comprehensively describing plasma levels, metabolism and excretion of (–)-ephedrine following IV injection. However, general but qualitative conclusions can be made based on PK studies of oral (–)-ephedrine to support clinical pharmacology information in the product label.

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.

The sponsor has not conducted any studies to evaluate the impact of intrinsic (Age, Sex, Race, Renal impairment, hepatic impairment) and extrinsic factors (drug-drug interactions). However, limited numbers of publications support some information in specific population.

The extent of metabolism of (–)-ephedrine to norephedrine are unknown as are the specific enzymatic or non-enzymatic pathways of metabolism. In addition, there are no publications evaluating metabolic/pharmacokinetic drug interactions with (-)-ephedrine.

The limited data with oral (–)-ephedrine suggests that urinary excretion may be a predominant pathway of elimination. Hence, impairment of renal function may affect renal clearance of ephedrine. However, the use of limited number of IV bolus doses of ephedrine on safety in patients with renal impairment is unclear. The recommended dosage for the treatment of clinically important hypotension in the setting of anesthesia is an initial dose of 5 to 10 mg administered by intravenous bolus. Whether an additional dose is needed after the initial dose will depend on the patient's clinical reponse of blood pressure. Since the product is given intravenously, the Cmax value will be similar for patients with different degrees of renal impairment. Therefore, even if the PK profile is different for patients with renal impairment, adjust the dose will not be an optioal since it will affect the Cmax value and consequently effectiveness of the product. Other safety concerns of administering IV ephedrine in patients with renal impairment may be addressed by the reviewing medical officer Dr. Amelia Luckett.

The sponsor did not conduct a study to evaluate the extent of IV (–)-ephedrine metabolism into norephedrine and also a hepatic impairment study was not conducted.

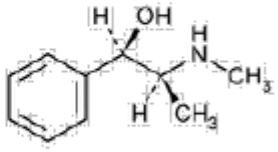
There is significant amount of safety and efficacy data supporting use of IV (–)-ephedrine in pregnant women during delivery (See review by medical officer Dr. Amelia Luckett). In addition, a study by Ngan Kee W. et. al. (2009) suggests that ephedrine crosses the placental barrier and enter the fetal blood circulation.

Overall, the submission is acceptable from a clinical pharmacology perspective.

2 QBR

2.1 General Attributes

The NDA 208289 was submitted by Flamel Ireland Limited to market, Ephedrine Sulfate Injection, USP which is the (–)-ephedrine isomer. The sponsor has not marketed the proposed product without Agency's approval; however, marketed unapproved formulations of ephedrine utilizing either the sulfate or hydrochloride salt exist in United States.

USAN	Ephedrine Sulfate USP
Chemical name	Benzenemethanol, α-[1-(methylamino)ethyl]-, [*R*-(*R**,*S**)]-, sulfate (2:1) (salt)
CAS number	134-72-5
Chemical structure	 H_2SO_4
Molecular formula	$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$
Molecular weight	428.54

The proposed product is a simple solution of Ephedrine Sulfate Injection, USP, is a sterile 50 mg/mL solution for injection to be given intravenously.

2.1.1 What is the Mechanism of Action?

As stated in the reputed textbook "Goodman and Gilman's: The pharmacological basis of therapeutics" (10th edition, 2001), ephedrine is a sympathomimetic agonist of both α- and β-adrenergic receptors. Ephedrine stimulates heart rate and increases cardiac output and variably increases peripheral resistance; as a result increases blood pressure.

2.1.2 What is the Proposed Indication?

Ephedrine sulfate is indicated for the treatment of clinically important hypotension in the setting of anesthesia.

2.1.3 What is the Proposed Dosage and Administration?

The proposed recommended dosage is an initial dose of 5 to 10 mg administered by intravenous bolus. Ephedrine sulfate may be administered as additional boluses as needed; not to exceed a total dosage of 50 mg.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical safety and efficacy studies?

The sponsor did not conduct specific clinical studies to assess the safety and efficacy of ephedrine sulfate for the proposed indication. However, considering the fact that ephedrine has been in use for decades, the sponsor submitted a number of publications in support of the proposed indication. Dr. Amelia Lucket's review addresses the clinical safety and efficacy of ephedrine used intravenously.

2.2.2 What are the pharmacodynamic (cardiovascular) effects of (-)-ephedrine?

Meng et. al. (2011) conducted a randomized two-treatment cross-over trial of one bolus dose of phenylephrine (100–200 mg) and one bolus dose of ephedrine (5–20 mg) were given to twenty nine ASA I–III elective surgery patients anaesthetized with propofol and remifentanil. The first treatment was given at least 10 min after the start of total IV anesthesia in order to achieve relatively stable blood propofol and remifentanil concentrations. If hypotension persisted for more than 10 min after the first treatment, the alternative agent (the one not chosen for the first treatment) was then administered. This second agent is referred to as the second treatment.

Figure: Pharmacodynamic profile of cardiovascular effects of (-)-ephedrine in one subject.	Figure: Measurements of cardiovascular effect of pre and post (-)-ephedrine treatments (n=29).	Summary of pre and post (-)-ephedrine treatment cardiovascular measurements.
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Source: Figure 1. Meng 2011a. Continuous MAP, CO, and SctO2 recordings from a selected patients	Source: Figure 2. Meng 2011a. Measurements of MAP, CO, and SctO2 for every patient.	Source: Table 1. Meng 2011a. MAP, mean arterial pressure; CO, cardiac output; HR, heart rate (beats min^{-1}); SV, stroke volume

An example of changes in mean arterial pressure (MAP), cardiac output (CO), and cerebral tissue oxygen saturation (Sct_{O2}) after one of the first ephedrine treatments is illustrated in Figure (left side), (D, E, F)respectively. MAP increased from the pretreatment level of ≈50 mm Hg to the highest level of ≈80 mm Hg within 2 min after ephedrine administration. However, CO remained unchanged at ≈5 litre min^{-1} and Sct_{O2} remained unchanged at ≈62%. The measurements of MAP, CO, and SctO2 before and after ephedrine treatment for every patient are presented in (middle figure below),

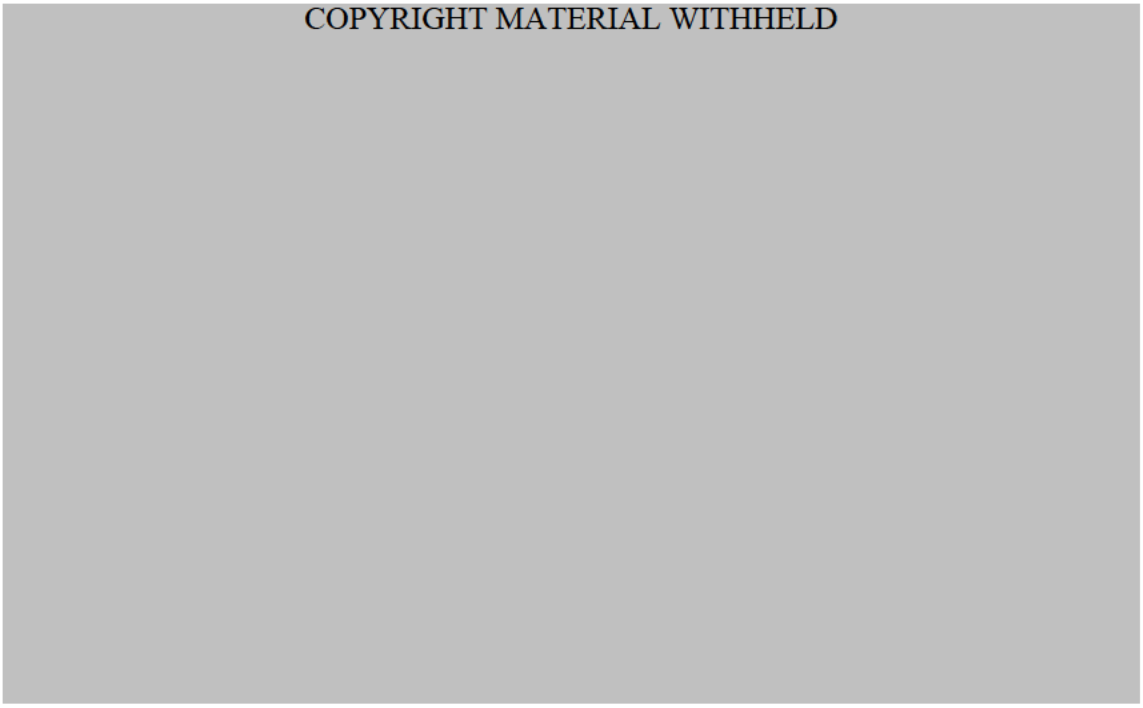
respectively. Grouped responses after the first and second ephedrine treatments are summarized in Table below. MAP was consistently increased after the first [ΔMAP=24.1 (13.5) mm Hg] and the second [ΔMAP=28.3 (13.3) mm Hg] ephedrine treatments. CO was slightly, but insignificantly, increased after the first [ΔCO=0.5 (1.7) litre min^{-1}] and the second [ΔCO=0.4 (0.9) litre min^{-1}] ephedrine treatments.

Dose-response of cardiovascular effects by (-)-ephedrine during C-section delivery.

Dose-related increase in systolic blood pressure and heart-rate have been reported following IV administration of (–)-ephedrine by Ngan Kee et. al. (2000).

A randomized, double-blind, dose-finding study of IV (-)-ephedrine for prevention of hypotension was performed in 80 women who received IV crystalloid preload solution for elective C-section delivery (Ngan Kee et al 2000). One minute after the spinal anesthesia was administered, subjects received saline placebo or (-)ephedrine 10, 20, or 30 mg IV. Hypotension, defined as a decrease in systolic arterial pressure (SAP) more than 20% below baseline and to below 100 mmHg, was treated with IV boluses of (-)-ephedrine 10 mg every minute as needed. Changes in the SAP in the first 12 minutes after the induction of spinal anesthesia are presented in Figure below. Note: the prophylactic use of ephedrine is not the subject of this NDA. The review of the manuscript was done to document the dose-related effects of ephedrine. Of particular note is the rebound hypertension in the 30 mg dose group.

Figure: Changes in Systolic Arterial Pressure After Administration of Intravenous (-)-ephedrine 10, 20 and 30 mg (Ngan Kee et. al. 2000)



2.2.3 What are the pharmacokinetic characteristics of (-)-ephedrine?

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 (-)[^{14}C]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.

2.3 Intrinsic Factors

The sponsor has not conducted any studies to evaluate the impact of intrinsic (Age, Sex, Race, Renal impairment, hepatic impairment). There are no publications describing pharmacokinetics of IV ephedrine in elderly, renal impairment or hepatic impairment patients, patients of different race and gender.

Renal impairment: Limited amount of urinary excretion data from publications, as described above, over the past four decades qualitatively indicate that ephedrine may be mainly eliminated in the urine. Renal disease is likely to impair the elimination of ephedrine, with a corresponding increase in elimination half-life, and renal insufficiency could lead to the accumulation of ephedrine, with multiple dose administration, to potentially result in toxic effects (Csjaka 2005, et. al., Brit J Clin Pharm 59(3): 335-345). On the other hand, due to the possible accumulation of ephedrine, if given as a multiple dose regimen, the dose requirement in patients with renal impairment may be lower. Additionally, patients with renal insufficiency often have cardiovascular issues and administration of drug with pressor effects such as ephedrine may cause constriction of the microvasculature in the kidney with unknown effects/safety in patients with renal impairment; hence caution should be exercised with use of ephedrine in patients with renal impairment.

Hepatic Impairment: Pharmacokinetics of ephedrine in hepatic impairment patients has not been studied. Ephedrine may be metabolized to norephedrine by unknown pathways of metabolism.

Age:

Elderly: Ephedrine appears 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.

Pediatrics: Pediatric plan for Akovaz was discussed at the PeRC meeting on 3/9/2016 and it was decided that studies in children younger than (b) (4) years can be waived because "there is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group, and the drug is not likely to be used by a substantial number of pediatric patients in that age group." Clinical safety and efficacy studies in children (b) (4) – 16 years age will be deferred. 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 (b) (4) 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.

Taguchi et. al. 1996 discusses changes in mean blood pressure in 0.4 – 14 year old children with 0.1 mg/kg and 0.2 mg/kg ephedrine. Most of the data in this publication is in children < 10 years age, with only 5 subjects in the >10 age. The discussion of these results is not appropriate as the age group is not under consideration for use of ephedrine.

In addition, the sponsor indicates that they were not able to confirm the source and identity (- or + enantiomer) of ephedrine.

Placental transfer of ephedrine: Ngan Kee W. et. al. (2009) evaluated blood levels of neurotransmitters, metabolic indicators, and ephedrine following 2 min infusion (at the rate of 60 ml/h of 8 mg/ml) ephedrine in women with term singleton pregnancies scheduled for elective Cesarean delivery under spinal anesthesia.

At the time of delivery, a 5- to 10-ml sample of maternal arterial (MA) blood was taken with a heparinized syringe by radial artery puncture. Immediately after delivery, samples of umbilical arterial (UA) and umbilical venous (UV) blood were taken from a double-clamped segment of cord.

The authors showed that ephedrine crosses the placenta, as evidenced by considerably greater values for UV/MA plasma concentration ratios (See table and figure below).

Table: Maternal and fetal concentrations of metabolic markers and ephedrine.	**Figure:** Ratio of UV/MA (A) and UA/UV (B) concentrations of ephedrine.
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Adapted from Table 3 and Figure 1 to delete phenylephrine data in Ngan Kee, W. et. al 2009 Anesthesiology 2009; 111:506–12.

2.4 Extrinsic Factors

The sponsor has not conducted any studies to evaluate the impact of extrinsic factors (drug-drug interactions) from a pharmacokinetics perspective. However, limited numbers of publications support some information as it relates to pharmacodynamic drug interactions with perioperative medications.

2.5 General Biopharmaceutics

Ephedrine Sulfate Injection, USP, is a sterile 50 mg/mL solution for injection to be given intravenously. The fill volume will be 1 mL in suitable glass vials with stopper closures. A slight overfill may occur to allow extraction of the labeled dose of 50 mg. USP reference quality calls for use of (-)-(1R,2S)-Ephedrine.

The only ingredient of Ephedrine Sulfate Injection, USP, is the active ephedrine sulfate in water for injection, USP.

Table: Description of ephedrine products used in publications supporting the NDA's clinical pharmacology submission.

Citation	+/-	Salt	Manufacturer	Contact History
Magalhaes et al. 2009	(-)	Sulfate	Cristalia	Magalhaes E indicated via email that he used ephedrine sulfate from Cristalia. A web document containing drug information indicates that Cristalia's product (Efedrin) contains "Ephedrine Sulfate (DCB 0458.03-1)". A web document from the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency) indicates that DCB 0458.03-1 corresponds to CAS 299-42-3. The CAS Registry number 299-42-3 corresponds to (1R,2S)-(−)Ephedrine.
Ngan Kee et al. 2000 Ngan Kee et al. 2008a Ngan Kee et al. 2009	(-)	Sulfate	DBL	Ngan Kee WD indicated via email that he used ephedrine sulfate from DBL in all studies. Hobbs P (an employee of Hospira) indicated via email that the product is (-)ephedrine.
Odagme et al. 2013	(-)	HCl	Martindale Pharma	Ogan S indicated via email that the ephedrine used was from Martindale Pharma. David Olatunya (an employee of Martindale Pharma) 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.
Vercauteren et al. 2000	(-)	HCl	Sterop	Vercauteren M indicated via email that he used ephedrine hydrochloride from Sterop in Belgium. An email from L Eykerman (an employee of Sterop) 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.
Videira et al. 2000	(-)	Sulfate	Cristalia	Videira R indicated via email that he used ephedrine sulfate from Cristalia. A web document containing drug information indicates that Cristalia's product (Efedrin) contains "Ephedrine Sulfate (DCB 0458.03-1)". A web document from the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency) indicates that DCB 0458.03-1 corresponds to CAS 299-42-3. The CAS Registry number 299-42-3 corresponds to (1R,2S)-(−)Ephedrine.
Wilkinson and Beckett 1968a	(-)	HCl	British Drug Houses	None; stated in paper
Yousefshahi et al. 2010	(-)	HCl	Sterop	Yousefshahi F indicated via email that the ephedrine used was ephedrine hydrochloride from Sterop. An email from L Eykerman (an employee of Sterop) 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.

Source: Table 6: 2.7.1 Summary of Biopharmaceutic Studies.

2.6 Analytical

Generally, the published articles cited in the NDA include limited information on the bioanalytical methods used in the studies.

Ngan Kee, W. et. al 2009 Anesthesiology 2009; 111:506–12: A sensitive method was developed for the analysis of ephedrine in plasma by using high-performance liquid chromatography-tandem mass spectrometry. Quantitation of the drug was performed by using multiple reaction monitoring (MRM) in positive ionization mode. Ephedrine was monitored at m/z 166 → 148 (API2000; Applied Biosystems, Foster City, CA). The internal standard, norephedrine HCl, was monitored at m/z 152 → 134. The limit of detection for ephedrine was 0.05 ng/ml, based on a signal-to-noise ratio of 3. Good linear response was obtained for ephedrine (0.05–500 ng/ml), with correlation coefficient value 0.9990. The within-day variation (intra-assay) of ephedrine ranged from 2.54% to 7.25% (mean 4.93%). The between-day variation (inter-assay) for ephedrine ranged from 4.41% to 8.03% (mean 6.14%).

Reference	Analytical Method
Beckett and Wilkinson 1965a	Urinary (-)ephedrine, methylephedrine, and norephedrine determined using method described in Beckett and Wilkinson 1965b
Berlin et al. 2001	Plasma ephedrine and norephedrine determined using the HPLC method described in Aymard et al. 2000
Csajka et al. 2005	Plasma (-)ephedrine and norephedrine determined using a method described in Haller et al. 2002
Gurley et al. 1998	Serum ephedrine determined using a modification of method described in Nieder and Jaeger 1988
Haller et al. 2002	Plasma ephedrine, pseudoephedrine, caffeine, norephedrine, methylephedrine, methylpseudoephedrine, and norpseudoephedrine determined using method described in publication
Persky et al. 2004	Plasma ephedrine determined using a proprietary, validated LC/MS/MS method (Oneida Research Services)
Pickup et al. 1976	Plasma ephedrine determined using gas chromatography method described in Pickup and Patterson 1974
Sever et al. 1975	Urinary ephedrine determined using method described in publication
Welling et al. 1971	Urinary ephedrine determined using gas chromatograph method described in publication
White et al. 1997	Serum ephedrine determined by HPLC using a modification of method Nieder and Jaeger 1988
Wilkinson and Beckett 1968a	Urinary ephedrine determined using method described in Beckett and Wilkinson 1965b
Wilkinson and Beckett 1968b	Urinary (-)ephedrine determined using method described in Beckett and Wilkinson 1965b

HPLC: High-performance liquid chromatography
LC/MS/MS: Liquid chromatography - tandem mass spectrometry

3 Labeling

(b) (4)

8.6 Renal Impairment

Ephedrine and its metabolite are excreted in urine. Patients with renal impairment (b) (4) 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.

12 Clinical Pharmacology

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]*.

Comments:

The following comments were communicated to the sponsor. Justify how the publications cited support the clinical pharmacology labeling. Check publications to confirm the drug substance used by authors was in fact (-)-ephedrine as proposed in your drug product. See the comments indicated in parenthesis. If appropriate publications cannot be submitted it may result in deletion of all material that is not supported.

The proposed labeling in section reads as follows in

12.3 Clinical Pharmacology:

Pharmacokinetics

(b) (4)

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

4.2 Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208289	**SDN**	1
Applicant	Flamel Ireland Ltd	**Submission Date**	6/30/2015
Generic Name	Ephedrine Sulfate Injection, USP	**Brand Name**	Ephedrine Sulfate Inj
Drug Class			
Indication	Treatment of clinically important hypotension in the setting of anesthesia.		
Dosage Regimen			
Dosage Form	IV Injection	**Route of Administration**	IV
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	8/28/2015	**74-Day Letter Date**	8/28/2015
Review Due Date	3/25/2016	**PDUFA Goal Date**	4/30/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☑ Metabolism Characterization		1	
☐ Transporter Characterization			
☑ Distribution		1	
☐ Drug-Drug Interaction		1	
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☑ Mass Balance Study		1	Sponsor submitted one publication to indicate predominant renal elimination of ephedrine. However, a renal impairment study was not conducted.
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects		1	
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			

Pharmacometrics					
☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies		**In Vitro**	2	**In Vivo**	2
Total Number of Studies to be Reviewed					

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	IV Injection
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	At the Pre-NDA meeting:CMC reviewer Dr. Ciby Abraham confirmed that ephedrine can only exist as a (-) enantiomer (Pre-NDA meeting). (b) (4) Bioanalytical methodology related publications are submitted.
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	Only publications documenting clinical experience with ephedrine were submitted.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a	☑Yes ☐No ☐N/A	Publications necessary for review of NDA have been submitted.

justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	Only publications documenting PK information were submitted.
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	Published clinical experience is submitted.
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
The clinical pharmacology and clinical database for this NDA is comprised of publications documenting clinical experience with parenteral ephedrine sulfate. Adequacy of these publications supporting the clinical pharmacology information of the product will be a NDA review issue.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
03/22/2016

YUN XU
03/22/2016

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/s/

SRIKANTH C NALLANI
08/26/2015

YUN XU
08/26/2015