CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208289Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number	NDA 208289
Priority or Standard	Standard
Submit Date	June 30, 2015
Received Date	June 30, 2015
PDUFA Goal Date	April 30, 2016
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products / Office of Drug Evaluation II
Reviewer Name	Amelia Luckett, MD
Review Completion Date	April 28, 2016
Established Name	Ephedrine Sulfate injection
(Proposed) Trade Name	Akovaz
Therapeutic Class	α- and β-adrenergic receptor agonist and norepinephrine-releasing agent
Applicant	Flamel Ireland Limited
Formulation	1 mL vial with 50 mg ephedrine sulfate
Dosing Regimen	Bolus intravenous injection 5 mg to 10 mg as needed, not to exceed 50 mg
Indication	Treatment of clinically important hypotension occurring in the setting of anesthesia
Intended Population	Adults

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 6

1.1 Recommendation on Regulatory Action 6
1.2 Risk Benefit Assessment 6
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ... 6
1.4 Recommendations for Postmarket Requirements and Commitments 6

2 INTRODUCTION AND REGULATORY BACKGROUND 7

2.1 Product Information 7
2.2 Tables of Currently Available Treatments for Proposed Indications 7
2.3 Availability of Proposed Active Ingredient in the United States 7
2.4 Important Safety Issues With Consideration to Related Drugs 8
2.5 Summary of Presubmission Regulatory Activity Related to Submission 8
2.6 Other Relevant Background Information 9

3 ETHICS AND GOOD CLINICAL PRACTICES 10

3.1 Submission Quality and Integrity 10
3.2 Compliance with Good Clinical Practices 10
3.3 Financial Disclosures 13

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 14

4.1 Chemistry Manufacturing and Controls 14
4.2 Clinical Microbiology 16
4.3 Nonclinical Pharmacology/Toxicology 16
4.4 Clinical Pharmacology 16
4.4.1 Mechanism of Action 16
4.4.2 Pharmacodynamics 16
4.4.3 Pharmacokinetics 16

5 SOURCES OF CLINICAL DATA 17

5.1 Tables of Studies 18
5.2 Review Strategy 18
5.3 Discussion of Individual Studies/Clinical Trials 19

6 REVIEW OF EFFICACY 19

Efficacy Summary 19
6.1 Indication 20
6.1.1 Methods 20
6.1.2 Demographics 24
6.1.3 Subject Disposition 25
6.1.4 Analysis of Primary Endpoints 25
6.1.5 Analysis of Secondary Endpoints 37

Reference ID: 3923762

6.1.6 Other Endpoints 37
6.1.7 Subpopulations 37
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 38
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 40
6.1.10 Additional Efficacy Issues/Analyses 40

7 REVIEW OF SAFETY 40

Safety Summary 40
7.1 Methods 41
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 41
7.1.2 Categorization of Adverse Events 43
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 44
7.2 Adequacy of Safety Assessments 44
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 44
7.2.2 Explorations for Dose Response 47
7.2.3 Special Animal and/or In Vitro Testing 47
7.2.4 Routine Clinical Testing 47
7.2.5 Metabolic, Clearance, and Interaction Workup 47
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 47
7.3 Major Safety Results 47
7.3.1 Deaths 47
7.3.2 Nonfatal Serious Adverse Events 47
7.3.3 Dropouts and/or Discontinuations 47
7.3.4 Significant Adverse Events 48
7.3.5 Submission Specific Primary Safety Concerns 48
7.4 Supportive Safety Results 48
7.4.1 Common Adverse Events 48
7.4.2 Laboratory Findings 53
7.4.3 Vital Signs 53
7.4.4 Electrocardiograms (ECGs) 53
7.4.5 Special Safety Studies/Clinical Trials 53
7.4.6 Immunogenicity 54
7.5 Other Safety Explorations 54
7.5.1 Dose Dependency for Adverse Events 54
7.5.2 Time Dependency for Adverse Events 54
7.5.3 Drug-Demographic Interactions 54
7.5.4 Drug-Disease Interactions 55
7.5.5 Drug-Drug Interactions 57
7.6 Additional Safety Evaluations 59
7.6.1 Human Carcinogenicity 59
7.6.2 Human Reproduction and Pregnancy Data 59
7.6.3 Pediatrics and Assessment of Effects on Growth 61

Reference ID: 3923762

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 61
7.7 Additional Submissions / Safety Issues 62

8 POSTMARKET EXPERIENCE 62

9 APPENDICES 63

9.1 Literature Review 63
9.2 Labeling Recommendations 63
9.3 Advisory Committee Meeting 66
9.4 Summaries of publications that support the efficacy of Akovaz 66
9.4.1 Adigun et al. 2010 66
9.4.2 Belzarena et al. 2006 67
9.4.3 Bhattarai et al. 2010 67
9.4.4 Ganeshanavar et al. 2011 68
9.4.5 Kansal et al. 2005 69
9.4.6 Kitchen et al. 2014 69
9.4.7 Lecoq et al. 2010 70
9.4.8 Meng et al. 2011—British Journal of Anaesthesia and Meng et al. 2011—Anesthesia Analgesia 71
9.4.9 Nag 2010 72
9.4.10 Ngan Kee et al. 2001 72
9.4.11 Ngan Kee et al. 2008 73
9.4.12 Nissen et al. 2010 74
9.4.13 Pennekamp et al. 2011 75
9.4.14 Prakash et al. 2010 76
9.5 Summary of publications that support the safety of Akovaz 78
9.6 References 139

Reference ID: 3923762

Table of Tables

Table 1 IRB/EC Approval and Informed Consent Information for Primary Efficacy Studies 10
Table 2 Clinical Trial Registration Information for Primary Efficacy Studies 12
Table 3 Summary of Investigator Information for Each Key Efficacy Study 12
Table 4 List of Investigators 13
Table 5 Comparison of Éclat's Proposed Formulation to Cited Manufactured Parenteral Formulations (per mL) 15
Table 6 Alphabetical list of published literature describing studies submitted in support of Akovaz 18
Table 7 Drug Product Identification for Clinical Efficacy Studies with Parenteral (-) Ephedrine Administration 21
Table 8 Citations that can be used to support the efficacy of Akovaz because the ephedrine product can be appropriately compared to Akovaz 23
Table 9 Demographics of subjects in publications that support the efficacy of Akovaz 24
Table 10 Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension 27
Table 11 Patients Undergoing Other Surgeries (Non-C-Section Delivery) Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension 34
Table 12 Patients Undergoing Surgery Under General Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension 35
Table 13 Ephedrine Dosing from Authoritative Texts for Treatment of Hypotension in the Setting of Anesthesia 38
Table 14 Summary of Hypotension Thresholds and (-)Ephedrine Doses to Support Dosing Recommendations 39
Table 15 Primary publications to support safety 42
Table 16 Supplementary publications to support safety 43
Table 17 Summary of ephedrine exposure in the publications submitted to support the safety of Akovaz 45
Table 18 Quantitative Adverse Event Data from Published Literature using Confirmed (-)Ephedrine for the Treatment of Hypotension 50
Table 19 Quantitative Adverse Event Data from Published Literature using Confirmed (-)Ephedrine for the Prevention of Hypotension 51
Table 20 Quantitative Adverse Event Data from Published Literature using Unconfirmed Ephedrine for the Treatment of Hypotension 52
Table 21 Reported Adverse Events for All Ephedrine Populations 52
Table 22 Summary of the Number of Treatment Studies with Interpretable Reports Relative to Fetal/Neonate Safety-Related Measures in Women Undergoing C-Section Delivery and Receiving Ephedrine for the Treatment of Hypotensive Episodes in an Anesthesia Setting 60
Table 23 Clinical review team changes: initial proposed Akovaz package insert compared to the current iteration of the package insert 64

Reference ID: 3923762

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data in the published literature, I recommend approval of Akovaz™ with revisions to the proposed labeling for the indication of treatment of clinically important hypotension occurring in the setting of anesthesia.

1.2 Risk Benefit Assessment

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)

Overall, Akovaz appears to be relatively safe for the treatment of hypotension in the setting of anesthesia with no deaths and only one serious adverse event noted in the publications submitted to support the safety of Akovaz. Even though ephedrine has been associated with the risk of hypertension and tachycardia, an episode of perioperative hypotension is associated with increased morbidity and mortality, whereupon the use of ephedrine in this situation results in a favorable risk: benefit assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety issues identified in the review of this application require postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant requested a partial waiver from pediatric studies for subjects aged 0 to (b)(4)-years-old and deferral of studies for subjects aged (b)(4) to 16-years-old. In a letter dated July 13, 2015, we agreed with this Initial Pediatric Study Plan.

Reference ID: 3923762

After further deliberation, the applicant will be granted partial waiver from pediatric studies for subjects aged 0 to 12-years-old and deferral of studies for pediatric subjects 12 to 16-years-old.

From a nonclinical pharmacology toxicology perspective, reproductive and developmental toxicology studies will be required as Postmarketing Requirements following the approval of the product. For more information, see the pharmacology toxicology review of this submission.

2 Introduction and Regulatory Background

2.1 Product Information

Ephedrine sulfate is currently a marketed unapproved drug. It has the chemical name (1R,2S)-(-)-2-methylamino-1-phenylpropan-1-ol sulfate and functions as both an α-adrenergic and β-adrenergic agonist. Flamel Ireland Limited intends to make this drug available in a 1 mL vial that contains 50 mg of ephedrine sulfate. The proposed package insert recommends dilution of Akovaz to 5 mg/mL in 5% Dextrose or 0.9% Sodium Chloride for intravenous bolus administration.

Flamel Ireland Limited proposes the trade name of Akovaz and the proposed indication of treatment of clinically important hypotension in the setting of anesthesia. The proposed population is in adults and the dosing regimen is to be bolus intravenous injection 5 mg to 10 mg as needed, not to exceed 50 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

NDA 203826 West-Ward Phenylephrine is approved for the indication of “increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.” (West-Ward_Pharmaceuticals December 2012)

NDA 204300 Éclat Vazculep (phenylephrine hydrochloride injection) has the indication of “treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.” (Eclat_Pharmaceuticals June 2014)

2.3 Availability of Proposed Active Ingredient in the United States

Ephedrine sulfate is currently a marketed unapproved drug in the United States.

Reference ID: 3923762

2.4 Important Safety Issues With Consideration to Related Drugs

The safety of ephedrine is discussed in section 7.0 of this review. Pseudoephedrine is an isomer of the drug product (-)-ephedrine. Pseudoephedrine is marketed as a nasal decongestant and is present in the Final Monograph 21 CFR 341. Product labels of pseudoephedrine contain the following warnings:

> 1. Do not take pseudoephedrine concomitantly with a monoamine oxidase inhibitor or for 2 weeks after discontinuing a monoamine oxidase inhibitor.
>
> 2. If you have heart disease, high blood pressure, thyroid disease, diabetes, or trouble urinating from an enlarged prostate, ask a doctor before taking pseudoephedrine.

Source: Product packaging for:

- CARE ONE® SUPHEDRINE NASAL DECONGESTANT NON DROWSY pseudoephedrine hydrochloride Maximum Strength 30 mg tablets distributed by American Sales Company (American_Sales_Company July 2009)
- EQUALINE® NASAL DECONGESTANT NON DROWSY MAXIMUM STRENGTH pseudoephedrine hydrochloride tablets, 30 mg distributed by SUPERVALU Inc. (Supervalu_Inc. October 2014)

The Akovaz package insert states that the pressor effect of Akovaz is increased in patients taking monoamine oxidase inhibitors and reactive hypertension is an adverse reaction in the proposed Akovaz package insert.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Submission of this NDA was initially discussed in Pre-IND 116266. Below is a table of key clinical issues discussed in meetings with the Applicant.

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

Reference ID: 3923762

Meeting/ Date	Key clinical issues
	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 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.

2.6 Other Relevant Background Information

Éclat was acquired by Flamel.

Reference ID: 3923762

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The contents of the submission were adequate for review of the safety and efficacy of Akovaz.

3.2 Compliance with Good Clinical Practices

Clinical studies were not performed for this NDA submission. However, the Applicant was able to obtain some information documenting compliance with Good Clinical Practice (GCP) for the literature references used to determine the efficacy of Akovaz. The Applicant reviewed literature references for evidence of Good Clinical Practice and sent a survey of Good Clinical Practice to literature reference authors.

Below are tables that demonstrate adherence to GCP. From this information, the Applicant concluded that these particular studies were conducted in accordance with Good Clinical Practice.

Table 1 IRB/EC Approval and Informed Consent Information for Primary Efficacy Studies

Citation	Country (City)	Institution	Informed Consent	Approval-Granting Institution
Adigun et al. 2010	Nigeria (Ibadan)	University College Hospital	Yes	University of Ibadan /University College Hospital joint Institutional Review Committee
Belzarena 2006	Brazil (Santana do Livramento)	Santa Casa de Santana do Livramento	Yes	Ethical Committee, Santa Casa de Misericórdia, Livramento
Bhattarai et al. 2010	India (Mangalore)	Lady Goschen Hospital	Yes[1]	Hospital research committee[2]
Dolci et al. 2011	Switzerland (Lausanne)	Centre Hospitalier Universitaire Vaudois	Yes	Clinical Research Ethics Committee
Ganeshanavar et al. 2011	India (Bagalkot)	S.N. Medical College and H.S. Hospital	Yes	Institutional ethics committee
Kansal et al. 2005	India (Delhi)	University College of Medical Sciences and Guru Teg Bahadur Hospital	Yes	Institutional ethics committee

Reference ID: 3923762

Citation	Country (City)	Institution	Informed Consent	Approval-Granting Institution
Kasaba et al. 2000	Japan (Miyazaki)	Miyazaki Medical College	Yes	Human Research Review Committee
Kitchen et al. 2014	Denmark (Copenhagen)	Rigshospitalet	Yes[2]	Regional ethical committee (H-1-2009-107)
Lecoq et al. 2010	Belgium (Liège)	Centre Hospitalier Universitaire de Liège	Yes	Institution Ethics Committee (CHU Liège, Belgium, ref: 2007–68)
Meersschaert et al. 2002	France (Paris)	Centre Hospitalier Universitaire Pitie-Salpetriere	Yes	Institutional ethical approval (CCPPRB Pitie-Salpetriere)
Meng et al. 2011a, Meng et al. 2011b	USA (Orange)	University of California, Irvine Medical Center	Yes	Institutional Research Board
Nag 2010	India (Belgaum)	KLES Prabhakar Kore Hospital & Medical Research Centre	Yes	Institutional ethical committee
Ngan Kee et al. 2001	China (Hong Kong)	Prince of Wales Hospital	Yes	Clinical Research Ethics Committee of the Chinese University of Hong Kong
Ngan Kee et al. 2008b	China (Hong Kong)	Prince of Wales Hospital	Yes	The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics
Nissen et al. 2010	Denmark (Copenhagen)	Rigshospitalet	Yes	Ethics Committee of Copenhagen (01-012/02)
Pennekamp et al. 2011	The Netherlands (Utrecht)	University Medical Centre Utrecht2	Yes	Ethics committee[3]
Prakash et al. 2010	India (Delhi)	Vardhman Mahavir Medical College and Safdarjang Hospital	Yes	Hospital ethics committee

[1] Author specifies that only "those who consented to the study were included"
[2] Information obtained from author via email
[3] Author indicated that "ethical approval was required and provided for the study" via email

(Source: NDA 208289 Applicant's table pages 10 and 11 of Summary of Clinical Efficacy)

Two of the publications referenced for efficacy were present in clinical trial databases:

Reference ID: 3923762

Table 2 Clinical Trial Registration Information for Primary Efficacy Studies

Citation	Country (City)	Trial Registry	Trial Number
Ngan Kee et al. 2008b	China (Hong Kong)	Clinical Trials Registry of the Centre of Clinical Trials, The Chinese University of Hong Kong	CUHK_CCT00080
Lecoq et al. 2010	Belgium (Liege)	EudraCT	2007–001143–22

(Source: NDA 208289 Applicant's table page 11 of Summary of Clinical Efficacy)

Although the Applicant also sent out a survey of GCP, responses were only received from Adigun, Belzarena, Bhattarai, Dolci, Ganeshanavar, and Lecoq. Additionally, it does not appear that all questions were answered by each investigator who responded to the survey.

Investigator information for the primary investigator or an alternative investigator for publications used to support efficacy were included in the NDA submission. Their names and associated publications are in the table below. The submitted investigator information has been reviewed and the investigators appear to be qualified.

Table 3 Summary of Investigator Information for Each Key Efficacy Study

Citation	Investigator	Table
Adigun et al. 2010	Olaitan A Soyannwo	Table 10
Belzarena 2006	Sergio D. Belzarena	Table 11
Bhattarai et al. 2010	Madhusudan Upadya	Table 12
Dolci et al. 2011	Mirko Nicolas Dolci	Table 13
Ganeshanavar et al. 2011	Anilkumar Ganeshnavar	Table 14
Kansal et al. 2005	Medha Mohta	Table 15
Kasaba et al. 2000	Mayumi Takasaki	Table 16
Kitchen et al. 2014	Niels H. Secher	Table 17
Lecoq et al. 2010	Jean-Pierre Lecoq	Table 18
Meersschaert et al. 2002	Pierre Coriat	Table 19
Meng et al. 2011a & Meng et al. 2011b	Maxime Cannesson	Table 20
Nag 2010	Kusha Nag	Table 21
Ngan Kee et al. 2001	Warwick D. Ngan Kee	Table 22
Ngan Kee et al. 2008b	Warwick D. Ngan Kee	Table 22
Nissen et al. 2010	Niels H. Secher	Table 17
Pennekamp et al. 2011	Frans L. Moll	Table 23
	Wolfgang Buhre	Table 24
Prakash et al. 2010	Smita Prakash	Table 25

(Source: NDA 208289 Applicant's table page 45 of Summary of Clinical Efficacy)

Reference ID: 3923762

3.3 Financial Disclosures

Financial disclosures were not submitted because no clinical studies were conducted by the Applicant for this NDA. However, the Applicant did include a table in which publications intended to support the efficacy of Akovaz are listed. The Applicant states that they have no financial arrangement with the investigators in these studies. This table is pictured below.

Table 4 List of Investigators

Title and Citation	Corresponding Author	Contact Information
Adigun et al. 2010	Dr. T.A. Adigun	(b) (4)
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. (b) (4)	
Prakash et al. 2010	Dr. Prakash	

(Source: NDA 208289 Applicant's table page 2 of Financial Certification and Disclosure)

Reference ID: 3923762

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The ability to make a scientific bridge between Flamel's ephedrine and the ephedrine product described in the literature is an important part of this NDA submission. In order to make this bridge, the Applicant was required to provide literature in which ephedrine as the (-) enantiomer is identified as the drug used in the study.

Flamel has provided information regarding the formulation differences between Flamel's ephedrine and the ephedrine product described in the literature submitted for this NDA. The purity of the ephedrine formulations in the submitted literature is largely unknown. However, if an ephedrine product is known to be USP, then it is considered to be 98% pure. Therefore, the ephedrine products used in the following publications can be considered to be 98% pure:

- Iqbal et al. 2010 (Iqbal and Khan 2010)
- Meng et al. 2011a and Meng et al. 2011b (Meng, Cannesson, et al. 2011; Meng, Tran, et al. 2011)

According to the CMC reviewer for this submission, if the labeling of an ephedrine product claims that the product therein conforms to a European Pharmacopoeia (Ph. Eur.) monograph, then it should be 99% to 101% pure. Therefore the ephedrine products used in the following publications may be considered to be likely 99% to 101% pure:

- Adigun et al. 2010 (Adigun, Amanor-Boadu, and Soyannwo 2010)
- Balcan et al. 2011 (Balcan 2011)
- Cooper et al. 2002 (Cooper et al. 2002)
- Cooper et al. 2007 (Cooper et al. 2007)
- Desalu and Kushimo 2005 (Desalu and Kushimo 2005)
- Dolci et al. 2011 (Dolci et al. 2011)
- Odagme et al. 2013 (Odagme MT 2013)

Flamel's ephedrine formulation and the ephedrine formulations in the submitted literature have comparable aqueous and pH range.

The table below compares Flamel's ephedrine product to the ephedrine products described in the literature submitted in support of this NDA submission. As confirmed by the Chemistry Manufacturing and Controls (CMC) review team for this application, all ephedrine formulations described in the table below are appropriately comparable to Flamel's ephedrine product.

Reference ID: 3923762

Table 5 Comparison of Éclat's Proposed Formulation to Cited Manufactured Parenteral Formulations (per mL)

Company	Ephedrine Salt	Quantity of Ephedrine Salt	Water for injection qs	Other Ingredients
Éclat	Sulfate	50 mg	Yes	Glacial acetic acid or sodium hydroxide (as (b) (4))
(b) (4)	Sulfate	50 mg	Yes	Sodium hydroxide and/or hydrochloric acid qs pH
	Sulfate	50 mg	Yes	N/A
	Sulfate	30 mg	Yes	Sodium chloride (b) (4)
	Hydrochloride	30 mg	Yes	Sodium chloride Dilute hydrochloric acid (b) (4)
	Hydrochloride	15 mg – 30 mg	Yes	N/A
	Hydrochloride	10 mg – 50 mg	Yes	Sodium chloride
	Hydrochloride	50 mg	Yes	N/A
	Hydrochloride	50 mg	Yes	(b) (4)

qs: sufficient quantity

(Source: NDA 208289 Applicant's table page 5 of Summary of Biopharmaceutic Studies)

The CMC review team contends that Flamel has submitted adequate information on the identity of the ephedrine products in the submitted literature publications that have manufacturers listed in table 5.

Although Akovaz is a product comprised of ephedrine sulfate, some of the publications submitted in support of this NDA are in the form of ephedrine hydrochloride instead of the ephedrine sulfate form.

There is a small difference in the amount of ephedrine base present in ephedrine sulfate when compared to ephedrine hydrochloride. A 50 mg dose of ephedrine sulfate contains 38 mg of ephedrine base. A 50 mg dose of ephedrine hydrochloride contains 41 mg of ephedrine base. This difference is small enough that a comparison of the dosing of ephedrine hydrochloride to ephedrine sulfate should not require additional calibration. For example, the proposed dose of Akovaz is a bolus of 5 to 10 mg. Five milligrams of ephedrine sulfate contains 3.8 mg of ephedrine base; 5 mg of ephedrine hydrochloride contains 4.1 mg of ephedrine base.

4.2 Clinical Microbiology

Clinical microbiology data were not submitted to this NDA because Akovaz is not a therapeutic antimicrobial drug.

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical studies of ephedrine were conducted for this NDA. Flamel instead relied upon scientific publications to support the nonclinical portion of the NDA. The Pharmacology/ Toxicology team intends to recommend approval of Akovaz with Postmarketing Requirements and pending agreement on labeling. For further information, see the Pharmacology Toxicology review of this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ephedrine is a direct agonist at the α-adrenergic receptor and an indirect agonist at the β-adrenergic receptor.

4.4.2 Pharmacodynamics

Ephedrine increases heart rate and usually blood pressure. The proposed package insert states:

> "Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure…The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, ß-2 adrenoceptor-mediated vasoconstriction, and ß-2 adrenoceptor-mediated vasodilatation. Stimulation of the ß-1 adrenoceptors results in positive inotrope and chronotrope action."

(Source: NDA 208289 applicant's proposed package insert)

The review team found this acceptable and the above statement will be included in the package insert.

4.4.3 Pharmacokinetics

(-)-Ephedrine taken orally is metabolized into norephedrine. Ephedrine and norephedrine are subsequently excreted in urine. A similar pathway for intravenous ephedrine is supported by limited data. Oral ephedrine has a plasma elimination half-life of about 6 hours.

Reference ID: 3923762

The Applicant did not conduct any studies to evaluate the impact of renal impairment on the pharmacokinetics of intravenous ephedrine. As concluded from some data with oral ephedrine, urinary excretion may represent the foremost means of elimination of intravenous ephedrine. Therefore, those with renal impairment would likely have decreased renal clearance of ephedrine. This likely decreased renal clearance would apply to both the active parent product (ephedrine) and the metabolite (norephedrine).

Although the pharmacokinetic parameters of intravenous ephedrine are unknown in patients with renal impairment, this lack of information can be mitigated by language in the package insert.

Theoretically, if renal clearance of intravenous ephedrine is decreased in those with renal impairment, there are two possible ways to lessen this effect:

1. Decrease the dose of ephedrine or
2. Decrease the frequency of ephedrine

Unfortunately, reducing the initial dose of ephedrine in those with known renal impairment is not an option because the effectiveness of ephedrine is dependent on the C_{max}. If the initial dose of ephedrine is decreased, the C_{max} will not be reached, rendering the product less effective.

Decreasing the frequency of ephedrine administration is something that can be accomplished, and, because ephedrine is a drug that is titrated to effect, this is already performed in clinical practice. For example: 5 mg of ephedrine may be given if a patient's blood pressure is low. After a sufficient period of time, if the patient's blood pressure continues to be low, another dose of ephedrine will be given. If, in patients with renal impairment, the effects of ephedrine persist, an additional bolus of ephedrine will not be necessary.

Language in the package insert to mitigate the risk to those with renal impairment in the package insert will read:

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

5 Sources of Clinical Data

No clinical trials were performed in support of this NDA submission. Only literature was submitted in support of this NDA.

5.1 Tables of Studies

Below is an alphabetical list of the published literature submitted in support of the safety and efficacy of this NDA. Full citations of these publications are in section 9.6 of this review:

Table 6 Alphabetical list of published literature describing studies submitted in support of Akovaz

Abdalla et al. 2014	Meng et al. 2011a
Adigun et al. 2010	Meng et al. 2011b
Balcan et al. 2011	Mokhtar and Sherif 2014
Belzarena 2006	Moran et al. 1991
Berends et al. 2005	Nag 2010
Bhattarai et al. 2010	Ngan Kee et al. 2000
Clark et al. 2005	Ngan Kee et al. 2001
Cooper et al. 2002	Ngan Kee et al. 2008a
Cooper et al. 2007	Ngan Kee et al. 2008b
Critchley et al. 1995	Ngan Kee et al 2009
Damevski et al. 2011	Nissen et al. 2010
Datta et al. 1982	Odagme et al. 2013
Defossez et al. 2007	Pennekamp et al. 2011
Desalu and Kushimo 2005	Prakash et al. 2010
Dhungana et al. 2008	Puri and Talwar 2010
Dolci et al. 2011	Ramanathan and Grant 1988
Dyer et al. 2009	Rehman et al. 2011
Foss et al. 2014	Simin et al. 2012
Ganeshanavar et al. 2011	Taguchi et al. 1996
Gunda et al. 2010	Taivainen 1991
Iqbal et al. 2010	Tanaka and Dohi 1994
Ishiyama et al. 2003b	Thomas et al. 1996
Kansal et al. 2005	Turkoz et al. 2002
Kasaba et al. 2000	Vercauteren et al. 2000
Kitchen et al. 2014	Videira et al. 2000
Lecoq et al. 2010	Wright et al. 1992
Magalhaes et al. 2009	Xu and Wang 2013
Meersschaert et al. 2002	Yousefshahi et al. 2010

5.2 Review Strategy

The Applicant relies entirely on published literature for the determination of safety, efficacy, and appropriate dosing of Akovaz. This published literature was divided by the Applicant into two categories:

1. Primary publications:

Reference ID: 3923762

Primary publications include 25 publications in which the applicant attempted to confirm that (-)-ephedrine enantiomer was used. Eighteen of these publications were submitted by the Applicant to support efficacy. An additional seven publications were added to this to support safety. These seven publications did not contain enough information to support efficacy. These publications studied hypotension in the setting of anesthesia.

2. Supplementary publications:
Supplementary publications include 21 publications in which ephedrine was used to treat hypotension but the (-)-ephedrine enantiomer could not be confirmed, and 15 publications in which ephedrine was used to prevent hypotension and the Applicant attempted to confirm that the (-)-ephedrine enantiomer was used.

See section 7.1.1 of this review for further detail of primary and supplementary publications.

With the assistance of the CMC review team for this submission, submitted publications were evaluated to determine if, in fact, the Applicant has adequately demonstrated that the ephedrine used in the publication was comparable to Akovaz.

5.3 Discussion of Individual Studies/Clinical Trials

Studies and trials described in publications submitted for this NDA and used to support the safety and efficacy of Akovaz are summarized in section 9 of this review.

6 Review of Efficacy

Efficacy Summary

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.

Reference ID: 3923762

6.1 Indication

The Applicant seeks the following indication for Akovaz:

> EPHEDRINE SULFATE INJECTION [redacted] (b) (4) for the treatment of clinically important hypotension in the setting of anesthesia

(Source: NDA 208289 page 2 of Akovaz proposed package insert)

6.1.1 Methods

In Table 5 on pages 6 and 7 of their Summary of Biopharmaceutic Studies, the applicant explains their strategy for determining the identity of the ephedrine product used to support efficacy. The purpose of including this table in this clinical review is to demonstrate the effort put forth by the Applicant to determine the identity of the ephedrine product in the publications submitted to support the efficacy of Akovaz. This table is pictured below.

Reference ID: 3923762

Table 7 Drug Product Identification for Clinical Efficacy Studies with Parenteral (-) Ephedrine Administration

Citation	+/-	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 containe "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.
Kansal et al. 2005	(-)	HCl		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.

Citation	+/-	Salt	Manufacturer	Contact History
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	(-)	Sulfate		Ngan Kee WD indicated via email that he used ephedrine sulfate from (b) (4) in all studies. (b) (4) (b) (4) indicated via email that the product is (-)ephedrine.
Ngan Kee et al. 2008b				
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.
Prakash et al. 2010	(-)	HCl		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.

(Source: NDA 208289 Applicant's Table 5 pages 6 and 7 of Summary of Biopharmaceutic Studies)

Because all of the ephedrine products in Table 5 in section 4.1 of this review are considered to be appropriately comparable to Flamel's ephedrine product, the literature submitted by Flamel presented in the table below is considered to be reliable to support the efficacy of ephedrine.

Table 8 Citations that can be used to support the efficacy of Akovaz because the ephedrine product can be appropriately compared to Akovaz

Citation	Salt	Manufacturer	# 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

Flamel identified three additional publications (in Table 7, above) that they thought could be used to support the efficacy of Akovaz:
1. Dolci et al. 2011
2. Kasaba et al. 2000
3. Meersschaert et al. 2002

However, Dolci et al. 2011, Kasaba et al. 2000, and Meersschaert et al. 2002 are inadequate to support the efficacy of Akovaz for the following reasons:

For Kasaba et al. 2000 and Meersschaert et al. 2002, the manufacturer of the ephedrine formulation used in the clinical study is unknown. For Dolci et al. 2011, (b) (4) was the ephedrine manufacturer used. As confirmed by the CMC review team, table 5 of this review lists ephedrine formulations that are appropriately comparable to Flamel's ephedrine product. Streuli is not a company listed in table 5 of this review.

All citations in Table 8 can be considered to support the efficacy of Akovaz. It should be noted that although the ephedrine products used in Nag 2010 and Pennekamp et al. 2011 were found to be comparable to Akovaz, they do not provide a high level of

Reference ID: 3923762

evidence because Nag 2010 was not published in a peer-reviewed journal and Pennekamp et al. 2010 was a letter to the editor.

Most of the clinical trials used to support the efficacy of Akovaz were not performed in the United States. Flamel attempted to provide evidence that these foreign clinical trials were performed with good clinical practice. Evidence pertaining to informed consent and IRB approval is summarized in section 3.2 of this review.

The publications submitted for efficacy are summarized and ephedrine in these publications is evaluated for the ability to increase blood pressure.

Individual publications submitted in support of efficacy are summarized in section 9.4 of this review. In these publications, 414 subjects received ephedrine. Dolci et al. 2011, Kasaba et al. 2000, and Meersschaert et al. 2002 are not included in section 9.4 of this review and are not used to evaluate the efficacy of Akovaz because the ephedrine product used in these publications was not determined to be comparable to Akovaz.

6.1.2 Demographics

Gender: Because the majority of studies submitted to support efficacy were in parturients, the majority of subjects are female. Approximately 371 of the 414 subjects in the publications submitted for assessment of efficacy are female.

Race and ethnicity: Race and ethnicity information was not present in any of the publications submitted for efficacy. However, the Applicant notes that it is probable that Ngan Kee at al. 2001 and Ngan Kee et al 2008b, conducted in China, had predominately Asian subjects. It is also probable that Nag 2010, Prakash et al. 2010, Ganeshanavar et al. 2011, Bhattarai et al. 2010, and Kansal et al. 2005, trials which took place in India, had subjects who were predominantly Indian. Adigun et al. 2010 was conducted in Nigeria and it is therefore likely that African subjects predominated.

Below is a table of additional demographics of publications submitted to support the efficacy of Akovaz.

Table 9 Demographics of subjects in publications that support the efficacy of Akovaz

Publication	# subjects receiving ephedrine	M/F subjects receiving ephedrine	Mean age of subjects receiving ephedrine ± SD (years)	Weight of subjects receiving ephedrine ± SD (kg)
Adigun et al. 2010	31	31 F	29.8 ± 3.3	64.96 ± 10.19
Belzarena 2006	38	38 F	34 ± 5	78 ± 10
Bhattarai et al. 2010	30	30 F	24.9 ± 3.5	55.20 ± 5.33
Ganeshanavar et al. 2011	30	30 F	22.7 ± 2.3	54.93 ± 4.62
Kansal et al. 2005	30	30 F	26.2 ± 4.0	53.7 ± 9.28

Publication	# subjects receiving ephedrine	M/F subjects receiving ephedrine	Mean age of subjects receiving ephedrine ± SD (years)	Weight of subjects receiving ephedrine ± SD (kg)
Kitchen et al. 2014	9	unknown	67 ± 3	84 ± 18
Lecoq et al. 2010	21	7M/ 14F	39	65 ± 10
Meng et al. 2011a	29	20M/ 9F	59 ± 13	
Meng et al. 2011b				
Nag 2010	50	50 F	26.9 ± 1.7	55.20 ± 5.33
Ngan Kee et al. 2001	23	23 F	32 ± 3	66 ± 10
Ngan Kee et al. 2008b	74	74 F	30 ± 4.3	unknown
Nissen et al. 2010	12	12 F	53 ± 19	unknown
Pennekamp et al. 2011	7	unknown	unknown	unknown
Prakash et al. 2010	30	30 F	24.5 ± 4.4	56.6 ± 6.7

6.1.3 Subject Disposition

The Applicant did not execute an examination of efficacy established on subject disposition. Most trials reported in the publications used to establish the efficacy of Akovaz had no dropouts among those who received ephedrine. It is unlikely that subject disposition had an impact on the evaluation of safety or efficacy of ephedrine in the publications submitted of support the efficacy of Akovaz.

6.1.4 Analysis of Primary Endpoints

To demonstrate efficacy, Flamel used the primary endpoint of an increase in blood pressure. Overall, clinical trials in the publications submitted to support the efficacy of Akovaz demonstrated ephedrine's ability to increase blood pressure. Endpoints for restoration of blood pressure were variable among clinical trials.

The Applicant states:

> For the purposes of this application, hypotension and related hemodynamic endpoints as defined by the authors will be used as the primary efficacy endpoint. The primary measures of efficacy identified in the primary literature involve measures of hypotensive events, degree of hypotension, number of pressor interventions needed to restore blood pressure to desired levels, time to hypotensive event or total time patient was hypotensive.

(Source: NDA 208289 page 6 of Summary of Clinical Efficacy)

The tables below are the applicant's tables. Rows displaying information from Dolci et al. 2011, Kasaba et al. 2000, and Meersschaert et al. 2002 have been deleted because the information they contain is not considered to be relevant because the identity of the

Reference ID: 3923762

ephedrine formulation used is unknown. The Applicant divided publications submitted to support the efficacy of Akovaz into three categories:

1. Randomized, double-blind, positive control in women having cesarean section with spinal anesthesia receiving intravenous (-)-ephedrine for the treatment of hypotension
   These publications are summarized in table 10 (below).
2. Randomized, double-blind, positive control in patients having surgeries (other than cesarean section) with spinal anesthesia receiving intravenous (-)-ephedrine for the treatment of hypotension
   This publication is summarized in table 11 (below).
3. Positive control trial in patients having surgery with general anesthesia receiving intravenous (-)-ephedrine for the treatment of hypotension
   These publications are summarized in table 12 (below).

The purpose of including these tables in this review is to demonstrate the efficacy of ephedrine in increasing blood pressure in the publications submitted in support of the efficacy of Akovaz. These tables describe the blood pressure threshold for initiation of ephedrine treatment, the magnitude of change in blood pressure after ephedrine administration, and the time course over which these changes in blood pressure occurred.

From the publications submitted to support the efficacy of Akovaz, it is difficult to draw decisive conclusions about the magnitude of blood pressure response to ephedrine based on the dose. From the descriptions in table 10, the following generalization may be made: In women having cesarean section with spinal anesthesia receiving (-)-ephedrine for the treatment of hypotension, ephedrine restores blood pressure.

From the descriptions in table 12, the following generalizations may be made: In patients having surgery under general anesthesia receiving (-)-ephedrine for the treatment of hypotension, when 5 to 20 mg of ephedrine is given for a decrease in MAP 10% to >20% or < 60 mmHg, the MAP is raised.

Reference ID: 3923762

Table 10 Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
Adigun et al. 2010 (Nigeria; Jul – Dec 2005) (-)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	Reported graphically only
			Phe (8)	Single 100 µg IV bolus	Increase in SBP above hypotension threshold reached by all patients Reported graphically only	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

(Source: NDA 208289 Applicant's table page 29 of Integrated Summary of Efficacy) Note: FB= Free base (Adigun, Amanor-Boadu, and Soyannwo 2010)

Note: To clarify 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. (Belzarena 2006)

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
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

(Source: NDA 208289 Applicant's table page 28 of Integrated Summary of Efficacy) Note: FB= Free base (Bhattarai, Bhat, and Upadya 2010)

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
Ganeshanavar et al. 2011 (India; Nov 2010 – Aug 2011) (-)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)	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
			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

(Source: NDA 208289 Applicant's table page 27 of Integrated Summary of Efficacy) Note: FB= Free base (Ganeshanavar A 2011)

Reference ID: 3923762

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
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

(Source: NDA 208289 Applicant's table page 30 of Integrated Summary of Efficacy) Note: FB= Free base (Kansal et al. 2005)

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
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 Total mean ± SD dose of Met = 3.1± 0.9 mg	All patients achieved efficacy endpoint Mean baseline SAP not reported Lowest recorded mean ±SD SAP = 92± 16 (range 58 – 120) Highest recorded mean ±SD SAP = 138± 16 (range 115 – 171)	Reported graphically only

(Source: NDA 208289 Applicant's table page 31 of Integrated Summary of Efficacy) Note: FB= Free base (Ngan Kee et al. 2001)

Reference ID: 3923762

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
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

(Source: NDA 208289 Applicant's table page 26 of Integrated Summary of Efficacy) Note: FB= Free base

Note: 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. (Ngan Kee, Khaw, et al. 2008)

Table 10 continued: Women Undergoing C-Section Delivery Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

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**
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) Mean ± SD Total Dose = 12.5 ± 5.1 mg {10.3 ± 4.2 mg FB}	Baseline SBP = 128±8 Hypotension Threshold = 100 (range 80 -112) Maximum SBP after Eph = 122 (range 110 – 140)	Reported graphically only
			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

(Source: NDA 208289 Applicant's table page 25 of Integrated Summary of Efficacy) Note: FB= Free base (Nag 2010) (Prakash et al. 2010)

Table 11 Patients Undergoing Other Surgeries (Non-C-Section Delivery) Under Spinal Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

Literature Citation (Study Site Location; Dates of Study Conduct)	**Efficacy Endpoint(s)**	**Hypotension Threshold Used for Initiation of Treatment**	**Treatment Groups**	**Dose/ Regimen**	**Post-Pressor Blood Pressure Changes**	
					Magnitude (mean mmHg values±SD)	**Time Course**
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

(Source: NDA 208289 Applicant's table page 38 of Integrated Summary of Efficacy. Reviewer has modified table to exclude the publication that will not be used for determination of efficacy of Akovaz) Note: FB= Free base (Lecoq et al. 2010)

Table 12 Patients Undergoing Surgery Under General Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

Literature Citation (Study Site Location; Dates of Study Conduct)	**Efficacy Endpoint(s)**	**Hypotension Threshold Used for Initiation of Treatment**	**Treatment Groups**	**Dose/Regimen**	**Post-Pressor Blood Pressure Changes**	
					Magnitude (mean mmHg values±SD)	**Time Course**
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	

(Source: NDA 208289 Applicant's table page 42 of Integrated Summary of Efficacy) Note: FB= Free base (Kitchen et al. 2014)

Table 12 continued: Patients Undergoing Surgery Under General Anesthesia Receiving Intravenous (-)Ephedrine for the Treatment of Hypotension

Literature Citation (Study Site Location; Dates of Study Conduct)	**Efficacy Endpoint(s)**	**Hypotension Threshold Used for Initiation of Treatment**	**Treatment Groups**	**Dose/Regimen**	**Post-Pressor Blood Pressure Changes**	
					Magnitude (mean mmHg values±SD)	**Time Course**
Meng et al. 2011a and Meng et al. 2011b (US; dates not stated) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	Increase in MAP ≥80% of baseline value or above 60 mmHg	Decrease in mean arterial pressure (MAP) > 20% or a MAP to < 60 mmHg	Eph (29) Note: 1 additional patient received Eph only but not included in reported analysis	5 – 20 mg {3.85 – 15.4 mg FB} IV bolus (single)	Baseline MAP not stated Hypotensive threshold MAP = 53 ± 12 Post-Eph MAP = 80 ± 13	Example presented graphically 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

(Source: NDA 208289 Applicant's table page 41 of Integrated Summary of Efficacy.) Note: FB= Free base (Meng, Cannesson, et al. 2011; Meng, Tran, et al. 2011; Nissen et al. 2010)

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

(Source: NDA 208289 Applicant's table page 42 of Integrated Summary of Efficacy) Note: FB= Free base

(Pennekamp et al. 2012)

Reference ID: 3923762

6.1.5 Analysis of Secondary Endpoints

No secondary endpoints were identified in this NDA submission.

6.1.6 Other Endpoints

No additional endpoints were identified in this NDA submission.

6.1.7 Subpopulations

As mentioned previously, publications submitted to support the efficacy of Akovaz were subdivided into the following subcategories:

1. Parturients undergoing spinal:
   - Adigun et al. 2010
   - Belzarena 2006
   - Bhattarai et al. 2010
   - Ganeshanavar et al. 2011
   - Kansal et al. 2005
   - Nag 2010
   - Ngan Kee et al. 2001
   - Ngan Kee et al. 2008
   - Prakash et al. 2010

2. Surgical patients undergoing spinal:
   - Lecoq et al. 2010

3. Surgical patients undergoing general anesthesia:
   - Kitchen et al. 2014
   - Meng et al. 2011a
   - Meng et al. 2011b
   - Nissen et al. 2010
   - Pennekamp et al. 2011

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)

Reference ID: 3923762

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Below is a table of ephedrine dosing for the treatment of hypotension in the setting of anesthesia identified by Flamel from textbooks.

Table 13 Ephedrine Dosing from Authoritative Texts for Treatment of Hypotension in the Setting of Anesthesia

Authoritative Recommendations	Ephedrine Dose
Barash PG, Cullen BF, Stoelting RK, Cahalan MS, Stock MC, Eds. 2009. Clinical anesthesia. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.	5-10 mg IV push
Martindale W. 1996. Martindale. The extra pharmacopoeia. 31st ed. Amer Pharmaceutical Assn.	3-6 mg IV push
Miller RD, Pardo M. 2011. Basics of anesthesia. 6th ed. Saunders.	5 to 10 mg IV
Hines RL, Marschall K. 2009. Stoelting's anesthesia and coexisting disease. 5th ed. Saunders.	5 to 10 mg IV
Aitkenhead AR, Rowbotham DJ, Smith G. 2006. Textbook of anaesthesia. 5th ed. Churchill Livingstone.	3-6 mg
Levinson G, Shnider SM. 1974. Vasopressors in obstetrics. Clinical Anesthesiology. 10:77-109.	5-25 mg (general statement) 2.5-5 mg (epidural block) 5-15 mg (epidural block) 5-15 (general statement, spinal anesthesia)
Barash PG, Estafanous G, Reves JG. 2001. Cardiac anesthesia: Principles and clinical practice. 2nd ed. Lippincott Williams and Wilkins.	5-10 mg IV
Levine WC, Allain RM, Alson TA, Dunn PF, Kwo J, Rosow CE. 2010. Clinical anesthesia procedures of the Massachusetts General Hospital. 8th ed. Lippincott Williams and Wilkins.	5-10 mg IV
Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL. 2009. Miller's anesthesia. Churchill Livingstone.	2.5-25 mg IV
Hamilton RJ. 2014. Tarascon pocket pharmacopoeia 2014 deluxe lab-coat edition. 15th ed. Tarascon.	10-25 mg IV

(Source: NDA 208289 Applicant's table page 15 of Clinical Overview)

Below is the Applicant's table summarizing (-)-ephedrine doses to support dosing recommendations. Orange rectangles have been used to designate rows displaying information from clinical trials not deemed to be relevant to this review because the identity of the ephedrine formulation used is unknown.

Table 14 Summary of Hypotension Thresholds and (-)Ephedrine Doses to Support Dosing Recommendations

Type of Anesthesia Patient Population	Blood Pressure Measure	(-)Ephedrine Bolus Dose; Number of Boluses or (Range of Boluses); Mean Total Dose	n	Threshold Used		Study Citation
				Percentage Decrease from Baseline	Absolute Threshold (mmHg)	
Spinal C-section delivery	Systolic blood pressure (SBP)	6 mg {4.9 mg FB} (1 – 3) Mean total dose = 8.4 mg {6.9 mg FB}	50	20	90	Nag 2010
		6 mg {4.9 mg FB} (1 – 4) Mean ± SD total dose = 12.5 ±5.1 {10.3 ± 4.2 mg FB}	30			Prakash et al. 2010
		6 mg {4.9 mg FB} (1 – 3) Mean ± SD total dose = 9.6 (4.6) mg {7.8 (3.7) mg FB}	30			Ganeshanavar et al. 2011
		5 mg {4.1 mg FB} Mean ± SD number of bolus doses = 2.5±0.5 Mean total dose = 12.5 mg {10.5 mg FB}	30			Bhattarai et al. 2010
		10 mg {7.7 mg FB} (1 – 3)	38			Belzarena 2006
		10 mg {7.7 mg FB} (1 to > 5)	74	None	100	Ngan Kee et al. 2008b
		5 mg {4.1 mg FB} single bolus	7	30	100	Adigun et al. 2010
		5 mg {4.1 mg FB} then infusion Mean ± SD total dose = 19.9± 11.5 {16.3 ± 9.4 mg FB}	30	20	100	Kansal et al. 2005
	Systolic arterial blood pressure (SAP)	10 mg {7.7 mg FB} then infusion Mean ± SD total dose = 50.0 ± 25.1 {38.5 ± 19.3 mg FB}	23	10	None	Ngan Kee et al. 2001
Spinal Non-C-section delivery	Mean arterial pressure (MAP)	7.5 mg {6.2 mg FB} single bolus	10	10	None	Dolci et al. 2011
		Up to 10 mg {8.2 mg FB} single bolus Mean ±SD total dose = 9.7 ± 0.3 mg {8.0 ± 0. 25mg FB}	21			Lecoq et al. 2010
General Wide range of surgery types		5 – 20 mg {3.85 – 15.4 mg FB} single bolus	29	20	60	Meng et al. 2011a and Meng et al. 2011b
		10 mg {8.2 mg FB} single bolus	12	None	60	Nissen et al. 2010
			9			Kitchen et al. 2014
		5 – 10 mg {4.1 – 8.2 mg FB} single bolus	7	20	None	Pennekamp et al. 2011
		5 mg {4.1 mg FB} (1 – 3)	9	10	None	Kasaba et al. 2000
		3 mg {2.5 mg FB} (1 – 2) Mean [95% CI] total dose = 6 [6-9] mg {4.9 (4.9 – 7.4) mg FB}	21	30	65	Meersschaert et al. 2002

(Source: NDA 208289 Applicant's table page 55 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 (above) and is

consistent with the ephedrine bolus dosing in the publications submitted to support efficacy.

In the package insert for Akovaz, the Applicant recommends that the total dosage of ephedrine not exceed 50 mg. The Applicant has based this recommendation on a maximum effective dose of 55 mg in the publication Saravanan et al. 2006 (Saravanan et al. 2006). The Applicant also states that recommendation of this maximum dose is based on the usual adult dose of ephedrine, which is 10 to 30 mg. (Source: NDA 208289 page 2 of Clinical Information Amendment September 22, 2015) The assertion that the usual adult dose of ephedrine is 10 to 30 mg is generally consistent with the mean total ephedrine dose in the publications submitted to support efficacy (table 14).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The time to onset of treatment effect has been evaluated by the Applicant. On this point, the Applicant states:

> The publications supporting the efficacy of (-)ephedrine for the target indication generally do not provide sufficient granularity of data to be able to specifically describe the timing of sequential doses of (-)ephedrine relative to changes in blood pressure after the initial dose is given.

(Source: NDA 208289 page 57 of Integrated Summary of Efficacy)

The Applicant does, however, provide a publication, Dyer et al. 2009, that describes the time to onset of the treatment effect of ephedrine. In this publication the mean time to peak mean arterial blood pressure after ephedrine administration was 89.8 seconds.

Evidence of the persistence of efficacy of intravenous ephedrine has not been submitted with the NDA. However, the Applicant did submit publications studying the pharmacokinetics of orally administered (-)-ephedrine.

Tachyphylaxis is known to occur with ephedrine (Morishita and Furukawa 1975). A statement about tachyphylaxis will be included in the Akovaz package insert.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

Safety Summary

Overall, Akovaz appears to be relatively safe for the treatment of hypotension in the setting of anesthesia with no deaths and only one serious adverse event noted in the publications submitted to support the safety of Akovaz.

7.1 Methods

In order to support the safety of Akovaz, Flamel intends to rely on 56 publications that are designated as “primary” or “supplementary.”

Primary publications include those in which the Applicant has attempted to confirm that the (-)ephedrine enantiomer used in the publication is comparable to Akovaz. Eighteen of these publications were submitted by the Applicant to support efficacy. An additional seven publications were added that did not contain enough information to support efficacy. These publications studied the treatment of hypotension in the setting of anesthesia. These publications are in Table 15 below in section 7.1.1 of this review.

Twenty-one supplementary publications include those in which the (-)ephedrine enantiomer could not be confirmed and documented. Fifteen supplementary publications include those in which ephedrine was used prophylactically and the applicant sought to confirm that the ephedrine product used in the publication was comparable to Akovaz. These publications are in Table 16 below in section 7.1.1 of this review.

Of the “primary” and “supplementary” publications submitted to support the safety of Akovaz, five publications are listed in both Table 15 and Table 16. The following publications are listed in both tables:

- Damevski et al. 2011
- Defossez et al. 2007
- Desalu and Kushimo 2005
- Ngan Kee et al. 2000
- Vercauteren et al. 2000

These publications are in both Table 15 and Table 16 “because they contain control patients who received ephedrine for treatment of hypotension and patients who were treated with ephedrine prophylactically.” (Source: NDA 208289 page 6 of Integrated Summary of Safety)

Some of the publications submitted to support the safety of Akovaz do not have a high level of evidence associated with them. For example, the publication Defossez et al. 2007 is in the format of an abstract only.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Below is a list of citations that the applicant considers as primary publications. We agree that the (-)-ephedrine enantiomer has been confirmed for these publications with the exception of those with an asterisk to the right of the citation.

Reference ID: 3923762

Table 15 Primary publications to support safety

18 primary publications submitted by the applicant to support both safety and efficacy	7 primary publications submitted by the applicant to support safety, but not efficacy
Adigun et al. 2010	Balcan et al. 2011*
Belzarena 2006	Damevski et al. 2011*
Bhattarai et al. 2010	Defossez et al. 2007
Dolci et al. 2011 *	Desalu and Kushimo 2005
Ganeshanavar et al. 2011	Ngan Kee et al. 2000
Kansal et al. 2005	Vercauteren et al. 2000
Kasaba et al. 2000*	Yousefshahi et al. 2010
Kitchen et al. 2014	
Lecoq et al. 2010	
Meersschaert et al. 2002 *	
Meng et al. 2011a	
Meng et al. 2011b	
Nag 2010	
Ngan Kee et al. 2001	
Ngan Kee et al. 2008b	
Nissen et al. 2010	
Pennekamp et al. 2011	
Prakash et al. 2010	

*It was determined by the CMC reviewer that the identity of (-)-ephedrine in these publications has not been confirmed.

For additional details of the safety information in the primary publications submitted by the Applicant, see section 9.5 of this review. The following publications designated as primary publications use an ephedrine product that has not been confirmed to be (-) ephedrine by the FDA CMC reviewer: Balcan et al. 2011, Damevski et al. 2011, Dolci et al. 2011, Kasaba et al. 2000, and Meersschaert et al. 2002.

Below is a list of supplementary publications. Twenty-one supplementary publications are included in which the (-)-ephedrine enantiomer could not be confirmed, but ephedrine was used to treat hypotension. Fifteen supplementary publications are included in which the applicant attempted to confirm that the ephedrine product used in the publication was comparable to Akovaz. For the column on the right, the (-)-ephedrine enantiomer has been confirmed for these publications with the exception of those with an asterisk to the right of the citation.

Reference ID: 3923762

Table 16 Supplementary publications to support safety

21 **supplementary** publications submitted by the Applicant to support safety; (-)ephedrine enantiomer could **not be confirmed** and documented; ephedrine used to **treat hypotension**	15 **supplementary** publications submitted by the Applicant to support safety; (-)ephedrine enantiomer **confirmed** by Applicant, but ephedrine was used **prophylactically**
Abdalla et al. 2014	Cooper et al. 2002
Berends et al. 2005	Cooper et al. 2007
Clark et al. 2005	Damevski et al. 2011 *,[2]
Critchley et al. 1995	Defossez et al. 2007 [2]
Datta et al. 1982	Desalu and Kushimo 2005 [2]
Dyer et al. 2009	Dhungana et al. 2008
Gunda et al. 2010	Foss et al. 2014*
Ishiyama et al. 2003b	Iqbal et al. 2010*
Mokhtar and Sherif 2014	Magalhaes et al. 2009
Moran et al. 1991	Ngan Kee et al. 2000 [2]
Puri and Talwar 2010	Ngan Kee et al. 2008a
Ramanathan and Grant 1988	Ngan Kee et al 2009
Rehman et al. 2011	Odagme et al. 2013
Simin et al. 2012	Vercauteren et al. 2000 [2]
Taguchi et al. 1996	Videira et al. 2000
Taivainen 1991	
Tanaka and Dohi 1994	
Thomas et al. 1996	
Turkoz et al. 2002	
Wright et al. 1992	
Xu and Wang 2013	

*It was determined by the CMC reviewer that the identity of (-)-ephedrine in these publications has not been confirmed
[2] Duplicative; also pictured in table 15 of this review

For additional details of the safety information in the supplementary publications submitted by the Applicant, see section 9.5 of this review.

7.1.2 Categorization of Adverse Events

The Applicant described adverse events in the publications submitted to support the safety of Akovaz.

Reference ID: 3923762

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data are pooled from publications submitted by the Applicant in the following ways:

1. Adverse events from publications in which the Applicant has attempted to confirm that the ephedrine in the publication is comparable to Akovaz and ephedrine in the publication is used to treat hypotension.
2. Adverse events from publications in which the Applicant has attempted to confirm that the ephedrine in the publication is comparable to Akovaz and ephedrine in the publication is used to prevent hypotension.
3. Adverse events from publications in which the Applicant has not proven or attempted to prove that the ephedrine in the publication is comparable to Akovaz and ephedrine in the publication is used to treat hypotension.
4. Adverse events from all publications submitted to support the safety of Akovaz.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure
As previously described, the Applicant submitted primary and supplementary literature to support the safety of Akovaz. Below is a reviewer-generated table comprised of information in the Applicant's tables on pages 79 and 80 of the Integrated Summary of Safety. The purpose of this table is to summarize the population, dose of ephedrine, and number of subjects who were given ephedrine in the primary and supplementary publications submitted to support safety.

Reference ID: 3923762

Table 17 Summary of ephedrine exposure in the publications submitted to support the safety of Akovaz

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] 2 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
(Source: NDA 208289 Applicant’s tables pages 79 and 80 of Integrated Summary of Safety. The above table was generated by this clinical reviewer, but all information was derived from the Applicant’s tables.)

Reference ID: 3923762

The doses to which subjects were exposed in these publications are consistent with the doses that the Applicant recommends for Akovaz.

Demographics

Subjects in the "primary" safety population, i.e., those being treated for hypotension with a formulation that is thought by the Applicant to be (-)-ephedrine contains mostly female patients having spinal anesthesia for cesarean section. Publications in table 15 are considered "primary" publications to support safety. It is acceptable to extrapolate to the rest of the population undergoing anesthesia because, 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)

Most subjects in the "primary" safety population had a BMI less than 30 kg/m^2.

Subjects in publications in the "primary" safety population mostly did not have race or ethnicity reported, except for Ngan Kee et al. 2000, in which it was specified that subjects were Asian. Most subjects in the "primary" safety population were ASA I or II, and were excluded if they had hypertension or poorly controlled hypertension. Most subjects in the "primary" safety population having cesarean section were excluded if they had diabetes, cardiovascular disease, neurologic disease, or obstetric complications.

Publications in table 16 are considered "supplementary" publications to support safety. Racial and ethnic group of the subjects is rarely stated in "supplementary" safety publications submitted to this application. An exception is Critchley et al. 1995 in which subjects are described as Chinese.

"Supplementary" publications included some subjects that were in alternate demographic cohorts. Four publications evaluated women with preeclampsia having cesarean section: Abdalla et al. 2014, Berends et al. 2005, Clark et al. 2005, and Mokhtar and Sherif 2014. Three publications evaluated elderly subjects: Critchley et al. 1995, Puri and Talwar 2010, and Taivainen 1991. Two publications included ASA III subjects: Critchley et al. 1995 and Taivainen 1991.

Elderly subjects were described in three publications in section 7.5.3 of this review.

Reference ID: 3923762

7.2.2 Explorations for Dose Response

An exploration for dose response of adverse events was not performed by the Applicant, nor does it appear possible to make an accurate assessment of adverse event incidence by dose due to the limited available data and the variation in dose received by subjects in the submitted publications.

7.2.3 Special Animal and/or In Vitro Testing

No nonclinical studies of ephedrine were conducted for this NDA. See section 4.3 of this review.

7.2.4 Routine Clinical Testing

See section 7.4.2, 7.4.3, and 7.4.4 of this review.

7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 2.4 of this review.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were noted in the publications submitted to support the safety of Akovaz.

7.3.2 Nonfatal Serious Adverse Events

Of the “primary” and “supplementary” publications submitted to support the safety of Akovaz, one serious adverse event was reported. This was reported in Ngan Kee et al. 2008b in which the neonate of a mother who received ephedrine was placed in the neonatal intensive care unit for feto-maternal transfusion syndrome. (Ngan Kee, Khaw, et al. 2008)

7.3.3 Dropouts and/or Discontinuations

An exploration of dropouts and discontinuations in the publications submitted to support the safety of Akovaz was not submitted by the Applicant. Subject disposition for publications used to support the efficacy of Akovaz (and also the safety) is described in

Reference ID: 3923762

section 6.1.3 of this review. Most additional publications submitted to support the safety of Akovaz did not describe dropouts or discontinuations.

7.3.4 Significant Adverse Events

Severe adverse events and adverse events leading to trial withdrawal are considered significant adverse events. Adverse events leading to trial withdrawal are described in section 7.3.3 of this review. In terms of severe adverse events, the Applicant did not analyze adverse events for severity. In the publications submitted to support safety, the following adverse events described as severe occurred in subjects after receiving ephedrine:

> Desalu and Kushimo 2005 described severe hypotension, but this was an expected result of the neuraxial technique described, and it occurred in subjects who were to be administered additional vasopressor. (Desalu and Kushimo 2005)
>
> In Ngan Kee et al. 2009, one maternal subject in the ephedrine treatment group had severe shivering, an adverse event that is frequently noted with spinal anesthesia. (Ngan Kee et al. 2009)

7.3.5 Submission Specific Primary Safety Concerns

The adverse events described in the publications submitted to support the safety of Akovaz did not raise unanticipated safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant summarized all adverse events from the publications submitted in support of the safety of Akovaz. Publications that did not note the frequency of an adverse event were not included in the analysis. Rounding was used if the frequency and the number of subjects experiencing an adverse event were not stated. The Applicant divided the publications into three categories for the purpose of reporting adverse events:

1. Publications in which Flamel believes they have confirmed that the ephedrine formulation is the (-)-ephedrine and this was used to treat hypotension. Adverse events in these publications are described in table 18.

2. Publications in which Flamel believes they have confirmed that the ephedrine formulation is the (-)-ephedrine and this was used for prevention of hypotension. Adverse events in these publications are described in table 19.

3. Publications in which Flamel does not believe they have confirmed that the ephedrine formulation is (-)-ephedrine and this was used to treat hypotension. Adverse events in these publications are described in table 20.

Reference ID: 3923762

Table 18 Quantitative Adverse Event Data from Published Literature using Confirmed (-)Ephedrine for the Treatment of Hypotension

		Nausea n (%)	**Vomiting** n (%)	**Bradycardia** n (%)	**Tachycardia** n (%)	**R-R Variability** n (%)	**Ventricular ectopics** n (%)	**Dizziness** n (%)	**Reactive Hypertension** n (%)	**Other** n (%)
Prakash et al. 2010	Eph (n=30)	4 (13%)	1 (3%)		13 (43%)					
Ngan Kee et al. 2008b	Eph (n=74)	13 (13%)								
Bhattarai et al. 2010	Eph (n=30)									Thumping heart: 3 (10%)
Adigun et al. 2010[a]	Eph (n=7)	4 (13%)							1 (3%)	
Kansal et al. 2005	Eph (n=30)	5 (17%)		1 (3%)		1 (3%)	1 (3%)	1 (3%)		Restlessness: 1 (3%)
Ngan Kee et al. 2001	Eph (n=23)	5 (22%)								
Ngan Kee et al. 2000[b]	Eph (n=20)	9 (45%)							2 (10%)	
Damevski et al. 2011[b]	Eph (n=20)	12 (60%)	10 (50%)							
Vercauteren et al. 2000[b]	Eph (n=24)	16 (67%)	1 (4%)							
TOTAL	**Ephedrine (n=258)**	**36 (14%)**	**12 (5%)**	**1 (0.4%)**	**13 (5%)**	**1 (0.4%)**	**1 (0.4%)**	**1 (0.4%)**	**3 (1%)**	**Thumping Heart: 3 (1%) Restlessness: 1 (0.4%)**
		32 (12%)								

[a] This reference refers to the adverse event as "hypertension" but reactive hypertension from pressor dose is implied. Hypertension is defined as an increase of blood pressure 30% above baseline

[b] Only the data from the control group who received (-)ephedrine for the treatment of hypotension (and did not receive prophylactic (-)ephedrine) are included.

(Source: NDA 208289 Applicant's table page 83 of Integrated Summary of Safety)

Table 19 Quantitative Adverse Event Data from Published Literature using Confirmed (-)Ephedrine for the Prevention of Hypotension

		Nausea n (%)	**Vomiting** n (%)	**Shivering** n (%)	**Reactive Hypertension** n (%)
Ngan Kee et al. 2000[a]	Eph-10mg (n=20)	9 (45%)			1 (5%)
	Eph-20mg (n=20)	13 (65%)			5 (25%)
	Eph-30mg (n=20)	5 (25%)			9 (45%)
Damevski et al. 2011[a]	Eph (n=20)	8 (40%)	6 (30%)		
Vercauteren et al. 2000 [a]	Eph (n=24)	9 (38%)	1 (4%)		
Iqbal et al. 2010	Eph-10mg (n=30)	12 (40%)	3 (10%)		
	Eph-15mg (n=30)	2 (7%)			4 (13%)
	Eph-20mg (n=30)				14 (47%)
Magalhaes et al. 2009[b]	Eph (n=30)	7 (23%)	4 (13%)		5 (17%)
Ngan Kee et al. 2008a[c]	Eph-8mg/mL (n=25)	10 (40%)			15 (60%)
Ngan Kee et al. 2009[c]	Eph (n=52)	18 (35%)			24 (47%)
Cooper et al. 2007[c,d]	Eph (n=27)				Post-anesthesia: 0-15 min: 9 (33%), 15- 30 min: 16 (59%)
Cooper et al. 2002	Eph (n=50)	15 (30%)	18 (36%)		
Odagme et al. 2013	Eph (n=29)			5 (17%)	1 (3%)
TOTAL	**Ephedrine (n=407)**	**53 (13%)**	**32 (8%)**	**5 (1%)**	**103 (25%)**
		55 (14%)			

[a] Only data from the prevention (those receiving (-)ephedrine before they became hypotensive) are included.
[b] Bradycardia defined as a heart rate less than 50 bpm.
[c] This reference refers to the adverse event as "hypertension" but since patients were treated with a continuous infusion of pressor agents this is considered reactive hypertension
[d] A total of patients experiencing hypertension from both the 0 – 15 min and 15 – 30 minute periods were included in the final total, with the acknowledgement that this may overestimate the number of patients who experienced hypertension.

(Source: NDA 208289 Applicant's table page 85 of Integrated Summary of Safety)

Table 20 Quantitative Adverse Event Data from Published Literature using Unconfirmed Ephedrine for the Treatment of Hypotension

		Nausea n (%)	Vomiting n (%)	Bradycardia n (%)	Tachycardia n (%)
Gunda et al. 2010[a]	Eph (n=50)	9 (18%)	7 (14%)	1 (2%)	8 (16%)
Dyer et al. 2009	Eph (n=18)	4 (22%)			
Moran et al. 1991	Eph (n=29)	8 (28%)			
Datta et al. 1982[b]	Eph-thresh (n=18)	12 (66%)			
	Eph-SBP-drop (n=20)	2 (10%)			
Rehman et al. 2011	Eph (n=23)	5 (14%)			
Turkoz et al. 2002	Eph (n=13)	10 (77%)			
Simin et al. 2012	Eph (n=33)	5 (15%)			
Xu and Wang 2013	Eph (n=60)	16 (27%)		1 (2%)	
Clark et al. 2005	Eph-Preeclamptic (n=17)	8 (47%)	1 (6%)	1 (6%)	
	Eph-Normotensive (n=20)	12 (60%)	6 (30%)	4 (20%)	
Taivainen 1991	Eph (n=15)	1 (7%)			
TOTAL	**Ephedrine (n=296)**	**45 (15%)**	**14 (5%)**	**7 (2%)**	**8 (3%)**
		45 (15%)			

[a] Tachycardia defined as an increase in heart rate > 30% above baseline values.
[b] Patients in the Eph-thresh group received ephedrine when they met the hypotensive threshold, while patients in the Eph-SBP-drop received ephedrine when any drop in SBP was detected. The patients in the latter group are not included in the adverse event total for this reason.

(Source: NDA 208289 Applicant's table page 86 of Integrated Summary of Safety)
Note: the numbers in the "total" row of table 19 do not "add up." This is likely because the 20 subjects in the Eph-SBP-drop group essentially received ephedrine prophylactically. Two of these subjects experienced nausea and vomiting.

Below is a table summarizing the adverse events from the three tables above.

Table 21 Reported Adverse Events for All Ephedrine Populations

	N=258 n(%)	**N=407 n(%)**	**N=296 n(%)**	**N=961 n(%)**
	Confirmed (-)Ephedrine, Treatment, Table 18	**Confirmed (-)Ephedrine, Prevention, Table 19**	**Unconfirmed Ephedrine, Treatment, Table 20**	**Overall**
Nausea n(%)	36 (14%)	53 (13%)	45 (15%)	134 (14%)
Vomiting n(%)	12 (5%)	32 (8%)	14 (5%)	58 (6%)
Nausea and/or Vomiting n(%)	32 (12%)	55 (14%)	45 (15%)	132 (14%)
Tachycardia n(%)	13 (5%)		8 (3%)	21 (2%)
Bradycardia n(%)	1 (0.4%)		7 (2%)	8 (1%)
Reactive Hypertension n(%)	3 (1%)	103 (25%)		106 (11%)
Thumping heart n(%)	3 (1%)			3 (0.3%)
Shivering n(%)		5 (1%)		5 (0.5%)
R-R Variability n(%)	1 (0.4%)			1 (0.1%)
Ventricular ectopics n(%)	1 (0.4%)			1 (0.1%)

	Confirmed (-)Ephedrine, Treatment, Table 18	Confirmed (-)Ephedrine, Prevention, Table 19	Unconfirmed Ephedrine, Treatment, Table 20	Overall
Dizziness n(%)	1 (0.4%)			1 (0.1%)
Restlessness n(%)	1 (0.4%)			1 (0.1%)
TOTAL n	258	407	296	961

(Source: NDA 208289 Applicant's table page 87 of Integrated Summary of Safety. This table has been modified by this clinical reviewer to suite the purposes of this review.)

Note that reactive hypertension was much more common in the publications in which ephedrine was used to prevent hypotension.

7.4.2 Laboratory Findings

Neither the "primary," nor the "supplementary" publications submitted to support the safety of Akovaz contained the results of chemistry labs, hematology labs, or urinalysis obtained at or after baseline.

7.4.3 Vital Signs

Pulse oximetry was included in all publications submitted to support the safety of Akovaz, but no treatment-related events were noted. Publications that were submitted to support the efficacy of Akovaz evaluated (-)-ephedrine's ability of increase blood pressure. The results of this analysis are in section 6.1.4 of this review.

7.4.4 Electrocardiograms (ECGs)

The Applicant did not analyze electrocardiogram data from publications. Tachycardia, bradycardia, R-R variability, thumping heart and ventricular ectopics have been addressed in section 7.4.1 of this review. Additional findings on electrocardiogram in subjects who received ephedrine were not described in the publications submitted in support of the safety of Akovaz.

In regard to a thorough QT study, the Division of Pharmacovigilance II performed a review of post-marketing adverse event reports and did not identify a signal. Further assessment has not been deemed necessary due to ephedrine's extensive history of use.

7.4.5 Special Safety Studies/Clinical Trials

No clinical or nonclinical studies were conducted by the Applicant in support of this NDA.

7.4.6 Immunogenicity

The Applicant did not provide information on the immunogenicity of ephedrine and it does not appear that there is readily available evidence that ephedrine is immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Applicant does not appear to have performed an assessment of adverse events based on dose. Performing such analysis would be difficult, if not impossible, because of the variation in clinical trials reported in the publications submitted to support the safety of Akovaz. In a publication studying ephedrine to prevent hypotension, a higher dose of ephedrine to prevent hypotension appears to be correlated with a higher incidence of hypertension. (Ngan Kee et al. 2000)

7.5.2 Time Dependency for Adverse Events

The Applicant does not appear to have performed an assessment of adverse events based on time from when ephedrine was given. Performing such analysis would be difficult, if not impossible, because of the variation in clinical trials reported in the publications submitted to support the safety of Akovaz.

7.5.3 Drug-Demographic Interactions

Due to considerable variation in the design of clinical trials and the dose of ephedrine administered in the publications submitted to support safety it is difficult, if not impossible, to observe meaningful variation in in adverse events by demographic group. While most of the publications submitted to support the safety of Akovaz involved the use of ephedrine during spinal anesthetic for cesarean section (and, therefore, the subjects were female and relatively young), three publications studied ephedrine in the elderly:

<u>Critchley et al. 1995</u>
This was a randomized, double-blind clinical trial conducted in Hong Kong in 30 ASA II or ASA III subjects aged 60 years or older with a fractured femur neck. Subjects were divided into two treatment groups, with 15 subjects in each treatment group. All subjects were given a spinal anesthetic with 0.5% bupivacaine followed by ephedrine 0.2 mg/kg and then by ephedrine infusion 0.5 mg/kg/hr. Treatment groups were distinguished from each other in that one treatment group received 3.5% polygeline 8 mL/kg over 2 to 4 minutes after spinal bupivacaine placement and the other did not. Subjects in the treatment group without colloid had a mean age of 79 years. Subjects in the colloid

Reference ID: 3923762

treatment group had a mean age of 74 years. The authors of Critchley et al. 1995 did not note adverse events in any subjects, and, thus, it is impossible to make conclusions about a correlation between adverse events and elderly patients. (Critchley et al. 1995)

Puri and Talwar 2010
This was a randomized, double-blind clinical trial conducted in India in 40 subjects over the age of 60 years having a urology procedure. Subjects were divided into two treatment groups:

1. Ephedrine bolus followed by infusion when hypotension occurred.
2. Mephentermine bolus followed by infusion when hypotension occurred.

All subjects were given a spinal anesthetic with 0.5% bupivacaine. Subjects were then given ephedrine or mephentermine to treat hypotension depending on the treatment group to which the subject was assigned. Subjects in the ephedrine treatment group had a mean age of 66.6 years. Subjects in the mephentermine treatment group had a mean age of 66.0 years. The authors of Puri and Talwar 2010 did not note adverse events in any subjects, and this, it is impossible to make conclusions about correlation between adverse events and elderly patients. (Puri 2010)

Taivainen 1991
This was a randomized, double-blind clinical trial conducted in Finland in 30 ASA II or ASA III subjects over the age of 65 years having hip surgery with spinal anesthesia. Subjects were divided into two treatment groups:

1. Ephedrine bolus when MAP decreased by more than 25% from reference
2. Etilefrine bolus when MAP decreased by more than 25% from reference

All subjects were given a spinal anesthetic with 0.5% bupivacaine, after which time subjects were given an ephedrine or etilefrine bolus to treat a decrease in MAP greater than 25%. Subjects in the ephedrine treatment group had a mean age of 74 years. Subjects in the etilefrine treatment group had a mean age of 75.2 years. The author of Taivainen 1991 noted only the adverse event of nausea in one subject in the ephedrine treatment group, making it impossible to make conclusions about correlation between adverse events and elderly patients. (Taivainen 1991)

7.5.4 Drug-Disease Interactions

In general, due to considerable variation in the design of clinical trials and the dose of ephedrine administered in the publications submitted to support safety it is difficult, if not impossible, to observe meaningful variation in in adverse events by disease state. However, four publications studied the use of ephedrine in subjects with preeclampsia and two publications that studied ephedrine in subjects who are American Society of Anesthesiologists Physical Status Classification III (ASA III).

7.5.4.1 Preeclampsia

Abdalla et al. 2014

This was a randomized, double-blind clinical trial conducted in Egypt in 40 subjects with preeclampsia having cesarean section with spinal anesthesia. Subjects were divided into two treatment groups:

1. Ephedrine bolus
2. Phenylephrine bolus

All subjects were given a spinal anesthetic with 0.5% bupivacaine and 0.5 mg morphine, after which time subjects were given an ephedrine or phenylephrine bolus to treat a 25% decrease in blood pressure from baseline or systolic blood pressure less than 90 mmHg. (Abdalla 2014)

Berends et al. 2005

This was a randomized clinical trial conducted in Belgium in 30 subjects with severe preeclampsia having cesarean section. Subjects were divided into three treatment groups:

1. Those given combined spinal epidural for anesthesia with fluid to prevent hypotension
2. Those given epidural anesthesia with fluid to prevent hypotension
3. Those given combined spinal epidural for anesthesia with ephedrine to prevent hypotension

All subjects were given ephedrine if hypotension occurred despite preventive measures (fluid or ephedrine). (Berends et al. 2005)

Clark et al. 2005

This was an open-label clinical trial conducted in the United Kingdom in 40 subjects having cesarean section with spinal anesthesia, half of whom had preeclampsia and half of whom were normotensive. Subjects with preeclampsia and subjects who were normotensive were given bolus intravenous ephedrine if blood pressure fell > 20% from baseline. (Clark, Sharwood-Smith, and Stewart 2005)

Mokhtar and Sherif 2014

This was a randomized clinical trial conducted in Egypt in 60 subjects with preeclampsia having cesarean section with spinal anesthesia. Subjects were divided into four treatment groups:

1. Ephedrine bolus for prevention immediately after spinal placement, then ephedrine bolus upon occurrence of hypotension
2. Phenylephrine bolus for prevention immediately after spinal placement, then phenylephrine bolus upon occurrence of hypotension.
3. Phenylephrine infusion immediately after spinal placement and titration of the infusion according to blood pressure
4. Lactated ringer bolus before spinal anesthetic and titration of infusion according to blood pressure

Subjects were given a spinal anesthetic with 0.5% bupivacaine with fentanyl followed by treatment according to treatment group. (Mokhtar 2014)

In Abdalla et al. 2014, it was noted that subjects in the ephedrine treatment group had an increased heart rate compared to those in the phenylephrine treatment group. No other adverse event information was noted. In Berends et al. 2005, an increase in the number of adverse did not appear to be correlated with ephedrine. In Clark et al. 2005, more subjects in the normotensive group required ephedrine than in the group with preeclampsia. More subjects in the normotensive group had nausea, vomiting, and bradycardia than in the preeclampsia group. In Mokhtar and Sherif 2014, subjects in the ephedrine treatment group had an increased heart rate compared to those in the phenylephrine treatment group.

The results of these clinical trials using ephedrine in those with preeclampsia do not demonstrate an increase in adverse events associated with use of ephedrine in the disease state preeclampsia.

7.5.4.2 American Society of Anesthesiologists Physical Status Classification III subjects

Both Critchley et al. 1995 and Taivainen 1991 have been summarized above in 7.5.3. Further information about subjects who were graded as ASA III is below.

1. Critchley et al. 1995: In the treatment group without colloid, 13 subjects were ASA II and two subjects were ASA III. In the colloid treatment group, 11 subjects were ASA II and four subjects were ASA III. The authors of Critchley et al. 1995 did not note adverse events in any subjects, and, thus, it is impossible to make conclusions about a correlation between adverse events and patients who are ASA III. (Critchley et al. 1995)

2. Taivainen 1991: In the ephedrine treatment group, eight subjects were ASA II and seven subjects were ASA III. In the etilefrine treatment group, seven subjects were ASA II and eight subjects were ASA III. The author of Taivainen 1991 noted only the adverse event of nausea in one subject in the ephedrine treatment group, making it impossible to make conclusions about correlation between adverse events and patients who are ASA III. (Taivainen 1991)

7.5.5 Drug-Drug Interactions

Drug-drug interactions have been addressed in the package insert for Akovaz. The review team agrees with the inclusion of these interactions and it is proposed that the table below appear in the package insert.

Interactions that Augment the Pressor Effect	
Oxytocin and oxytocic drugs	
Clinical Impact:	Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine). Some of these patients experienced a stroke.

Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.
Clonidine, propofol, monoamine oxidase inhibitors (MAOIs), atropine	
Clinical Impact:	These drugs augment the pressor effect of ephedrine.
Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs.
Interactions that Antagonize the Pressor Effect	
Clinical Impact:	These drugs antagonize the pressor effect of ephedrine.
Intervention:	Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs.
Examples:	α-adrenergic antagonists, β-adrenergic receptor antagonists, reserpine, quinidine, mephentermine
Other Drug Interactions	
Guanethidine	
Clinical Impact:	Ephedrine may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness.
Intervention:	Clinician should monitor patient for blood pressor response and adjust the dosage or choice of pressor accordingly.
Rocuronium	
Clinical Impact:	Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction.
Intervention:	Be aware of this potential interaction. No treatment or other interventions are needed.
Epidural anesthesia	
Clinical Impact:	Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia.
Intervention:	Monitor and treat the patient according to clinical practice.
Theophylline	
Clinical Impact:	Concomitant use of ephedrine may increase the frequency of nausea, nervousness, and insomnia.
Intervention:	Monitor patient for worsening symptoms and manage symptoms according to clinical practice.
Cardiac glycosides	
Clinical Impact:	Giving ephedrine with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias.
Intervention:	Carefully monitor patients on cardiac glycosides who are also administered ephedrine.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity evaluations are not required because this product is for acute use only.

7.6.2 Human Reproduction and Pregnancy Data

Ephedrine has been, and continues to be, used frequently for the treatment of hypotension in the setting of spinal anesthesia for cesarean section. This is confirmed by the recently published Practice Guidelines for Obstetric Anesthesia in Anesthesiology which states:

- “Either IV ephedrine or phenylephrine may be used for treating hypotension during neuraxial anesthesia.
- In the absence of maternal bradycardia, consider selecting phenylephrine because of improved fetal acid-base status in uncomplicated pregnancies”

('Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology' 2016)

Ephedrine is known to cross the placenta. The Applicant analyzed the neonatal effect of ephedrine in the publications submitted to support the safety of Akovaz in which women having cesarean section received ephedrine for the treatment of hypotension in the setting of anesthesia. This was accomplished by examining, among other things, risk of neonatal death and Apgar score in this neonatal population. Apgar of ≥7 at 5 minutes after delivery is thought to represent a healthy neonate. Publications were included in this analysis only if the specific Apgar score was reported, not the mean Apgar score. In all but one of the publications analyzed, Apgar scores were ≥7 at 5 minutes after delivery. The publication analyzed in which one of the neonates had an Apgar score < 7 at 5 minutes after delivery was Clark et al. 2005. Clark et al. 2005 is a trial of mothers with severe preeclampsia. In the severe preeclampsia treatment group, one neonate had an Apgar score < 7 at 5 minutes after delivery.

Another possible way to monitor neonatal well-being is by measurement of umbilical arterial and venous blood gases. Fetal hypoxia may be manifest as low umbilical artery pH.

Below is the table of publications that were examined by the Applicant to evaluate safety in neonates when ephedrine is given to women undergoing cesarean section.

Table 22 Summary of the Number of Treatment Studies with Interpretable Reports Relative to Fetal/Neonate Safety-Related Measures in Women Undergoing C-Section Delivery and Receiving Ephedrine for the Treatment of Hypotensive Episodes in an Anesthesia Setting

Fetus/Neonate Safety Related Measure(s)	Primary (-)Ephedrine Literature Reports (n = 15 Possible Studies) (Number of Patients)	Supplementary Ephedrine Literature Reports (n = 15 Possible Studies) (Number of Patients)
Apgar Scores Only	6 studies Nag 2010 (n = 50) Bhattarai et al. 2010 ((n = 30) Adigun et al. 2010 (n = 7) Belzarena 2006 (n = 38) Damevski et al. (n = 20 Desalu and Kushimo 2005 (n = 30)	8 studies Gunda et al. 2010 (n = 50) Dyer et al. 2009 (n = 18) Datta et al. 1982 (n = 18) Turkoz et al. 2002 (n = 13) Abdalla et al. 2014 (n = 20) Clark et al. 2005 (n=40) Ramanathan and Grant 1988 (n = 40)[b] Wright et al. 1992 (n = 17)[b]
Neurobehavioral Rating Scale Scores Only	0	0
Categorical Umbilical Artery pH Values Only	0	0
Apgar Scores PLUS Neurobehavioral Scores AND/OR Categorical Umbilical Artery pH Values	8 studies Prakash et al. 2010 (n = 30) Kansal et al. 2005 (n = 30)[a] Ngan Kee et al. 2001 (n = 23)[a] Ngan Kee et al. 2000 (n =20) Vercauteren et al. 2000 (n = 24) Balcan et al. 2011 (n = 41) Yousefshahi et al 2010 (n = 40) Ngan Kee et al. 2008b (n =74)	4 studies Thomas et al. 1996 (n = 20) Moran et al. 1991 (n = 29) Simin et al. 2012 (n = 33) Mokhtar and Sherif 2014 (n = 15)

[a] Includes initial IV bolus followed by IV infusion dosing regimen
[b] Epidural anesthesia (all other studies were spinal anesthesia)

(Source: NDA 208289 Applicant's table page 99 of Integrated Summary of Safety)

Cases of low umbilical artery pH in the neonate of a maternal patient who received ephedrine during cesarean section have been reported in the publications submitted to support the safety of Akovaz. The following publications detected low umbilical artery pH in the ephedrine treatment group:

- Kansal et al. 2005 had three infants with umbilical artery pH < 7.2 in the ephedrine treatment group. Five infants in the mephentermine treatment group had umbilical artery pH < 7.2. (Kansal et al. 2005)
- Ngan Kee et al. 2000 was a clinical trial in which three treatment groups received prophylactic ephedrine, and one treatment group received only bolus rescue ephedrine to treat hypotension. In the bolus rescue treatment group, two neonates had umbilical artery pH < 7.2. Some neonates in the prophylactic

ephedrine treatment groups also had umbilical artery pH < 7.2. (Ngan Kee et al. 2000)

- Ngan Kee et al. 2001 had nine infants with umbilical artery pH < 7.2 in the ephedrine treatment group. No subjects in the metaraminol treatment group had umbilical artery pH < 7.2. (Ngan Kee et al. 2001)
- Ngan Kee et al. 2008b had two neonates in the ephedrine treatment group with umbilical artery pH < 7.0 and no neonates in the phenylephrine treatment group with umbilical artery pH < 7.0 (Ngan Kee, Khaw, et al. 2008)
- Thomas et al. 1996 had one infant with umbilical artery pH <7.2 in the ephedrine treatment group compared with no infants in the phenylephrine treatment group. (Thomas et al. 1996)

7.6.3 Pediatrics and Assessment of Effects on Growth

No information was provided by the Applicant regarding the effect of ephedrine on growth in pediatric patients and no information had been located reported such effects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant asserts that there are no literature reports of overdose of intravenous bolus ephedrine. A brief search in PubMed confirms this finding. It would be logical that an overdose of intravenous ephedrine would cause increased heart rate and blood pressure.

The Applicant states that there are no literature reports of abuse of intravenous ephedrine in the setting of anesthesia and that the risk of abuse is low because:

> "1. In an anesthesia setting it is being used acutely for the management of hypotensive episodes and not for its other stimulant properties
> 2. It is intended as a prescription only medication
> 3. It will be primarily dispensed in a hospital formulary/pharmacy setting
> 4. The commercial product is intended as a single use vial provided as 50 mg in 1 mL WFI (not as a lyophilized product)"

(Source: NDA 208289 page 101 of Integrated Summary of Safety)

At the Pre-IND stage of this product's development, ephedrine was assessed by Controlled Substance Staff who noted that although ephedrine is not a controlled substance, it is a LIST 1 Chemical controlled by DEA because it can be used as a precursor in the manufacture of methamphetamine.

An abuse potential assessment was performed by the Applicant, after which the Applicant proposed that Akovaz "not be scheduled under the Controlled Substances

Reference ID: 3923762

Act." (Source: NDA 208289 page 1 of Multiple Module Information Amendment) I agree with the Applicant's assessment.

Withdrawal and rebound do not appear to be associated with ephedrine.

7.7 Additional Submissions / Safety Issues

On October 28, 2015 the applicant submitted a 120-day safety update. In this update, the Applicant states that a clinical literature search was performed to identify literature on intravenous ephedrine published after October 10, 2013. Seven clinical publications were identified that contained new safety information. The Applicant assessed these publications and concluded that "no new adverse events, unexpected severity of known events, or unexpected serious or clinically important safety findings associated with the use of ephedrine have been reported in the literature." (Source: NDA 208289 page 4 of Integrated Summary of Safety (120-day Safety Update))

8 Postmarket Experience

Ephedrine currently exists as a marketed unapproved drug. FAERS data was submitted by the Applicant and an analysis of FAERS data was conducted for the purpose of this NDA review by the Division of Pharmacovigilance. For further information on the analysis of FAERS data performed for the purpose of this NDA submission, see the review of ephedrine FAERS data performed by the Division of Pharmacovigilance.

Reference ID: 3923762

9 Appendices

9.1 Literature Review

This NDA submission has relied entirely on review of the literature. Description of the literature submitted to support the efficacy of Akovaz is described in section 6.0 of this review. Description of the literature submitted to support the safety of Akovaz is described in section 7.0 of this review.

9.2 Labeling Recommendations

Negotiations are currently underway for a finalized package insert. From the Akovaz package insert initially proposed to the present iteration of the package insert, clinical review team changes to the Full Prescribing Information were made that are described in the table below.

Table 23 Clinical review team changes: initial proposed Akovaz package insert compared to the current iteration of the package insert

Section	Language in initially proposed package insert	Language in current iteration of package insert
WARNINGS AND PRECAUTIONS	(b) (4)	Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine) [see Drug Interactions (7)]. Some of these patients (b) (4) stroke. Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.
WARNINGS AND PRECAUTIONS		*Tolerance and Tachyphylaxis* Data indicate that repeated administration of ephedrine can result in tachyphylaxis. Clinicians treating anesthesia-induced hypotension with AKOVAZ (ephedrine sulfate injection) should be aware of the possibility of tachyphylaxis and should be prepared with an alternative pressor to mitigate unacceptable responsiveness.
WARNINGS AND PRECAUTIONS		*Risk of Hypertension When Used Prophylactically* When used to prevent hypotension, ephedrine has been associated with an increased incidence of hypertension compared with when ephedrine is used to treat hypotension.
USE IN SPECIFIC POPULATIONS		*Renal Impairment* Ephedrine and its metabolite are excreted in urine. Patients with renal impairment (b) (4) excretion of ephedrine 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.

Section	Language in initially proposed package insert	Language in current iteration of package insert
OVERDOSAGE	(b) (4) can cause a rapid rise in blood pressure.	Overdose of ephedrine can cause a rapid rise in blood pressure. In the case of an overdose, careful monitoring of blood pressure is recommended. If blood pressure continues to rise to an unacceptable level, parenteral antihypertensive agents can be administered at the discretion of the clinician.
CLINICAL STUDIES	The evidence for the efficacy of EPHEDRINE (b) (4) INJECTION (b) (4) is derived from the published literature. Increases in blood pressure following administration of ephedrine were observed in (b) (4) literature (b) (4) studies, including 9 where ephedrine was used in pregnant women undergoing neuraxial anesthesia during cesarean delivery, (b) (4) in non-obstetric surgery under neuraxial anesthesia, and (b) (4) studies in patients undergoing surgery under general anesthesia. Ephedrine has been shown to raise systolic and mean blood pressure when administered as a bolus dose following the development of hypotension during anesthesia.	The evidence for the efficacy of ephedrine injection is derived from the published literature. Increases in blood pressure following administration of ephedrine were observed in 14 studies, including 9 where ephedrine was used in pregnant women undergoing neuraxial anesthesia during Cesarean delivery, 1 study in non-obstetric surgery under neuraxial anesthesia, and 4 studies in patients undergoing surgery under general anesthesia. Ephedrine has been shown to raise systolic and mean blood pressure when administered as a bolus dose following the development of hypotension during anesthesia.

(b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

9.4 Summaries of publications that support the efficacy of Akovaz

9.4.1 Adigun et al. 2010

Adigun et al. 2010	**(Efficacy, Safety)**
Citation:	Adigun TA, Amanor-Boadu SD, Soyannwo OA. 2010. Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective Caesarean section under spinal anaesthesia. Afr J Med med Sci. 39(1):13-20.
Country:	Nigeria
Study Design:	Randomized, double-blind, controlled study
Procedure:	Elective C-section delivery
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	31 females Mean age: 29.77 ± 3.32 years Mean weight: 64.96 ± 10.19 kg
(-)**Ephedrine Dose, Administration:**	Bolus intravenous (-)ephedrine 5 mg
Comparator:	Bolus intravenous phenylephrine 100 µg (n = 31)
Efficacy Results:	Results showed that the incidence rate of hypotension in the 62 subjects was 24.2%. Both vasopressors effectively restored both the systolic and the diastolic blood pressures. However, the mean systolic blood pressure (SBP) was higher in the phenylephrine group up to the 25th minute of the procedure.
Efficacy Conclusion:	(-)Ephedrine is safe and can be used as effectively as phenylephrine.
Safety Findings:	There was significant difference in heart rate (HR) between the 2 groups. All subjects showed an increase in HR in the (-)ephedrine group due to its beta adrenoreceptor activity. Nausea occurred in both groups and was found in hypotensive subjects; no subject vomited during the procedure. The mean Apgar scores were similar for the 2 groups; no baby had an Apgar score of <8 in either group.

(Source: NDA 208289 Applicant's table page 10 of Synopses of Individual Studies)

9.4.2 Belzarena et al. 2006

Belzarena 2006	**(Efficacy, Safety)**
Citation:	Belzarena SD. 2006. Ephedrine and etilefrine as vasopressor to correct maternal arterial hypotension during elective cesarean section under spinal anesthesia. Comparative study. Rev Bras Anestesiol. 56(3):223-229.
Country:	Brazil
Study Design:	Randomized, double-blind, parallel, positive control
Procedure:	Elective C-section
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	38 females Mean age: 34 ± 5
(-)**Ephedrine Dose, Administration:**	10 mg IV bolus when there was a decrease in SBP or mean blood pressure ≥ 20 mmHg
Comparator:	2 mg IV bolus etilefrine (n=41)
Efficacy Results:	22 (58%) received a single bolus of (-)ephedrine, while 27 (66%) received a single bolus of etilefrine. An increase in SBP above hypotension threshold reached by all patients.
Safety Findings:	Safety results (reactive hypertension, tachycardia, bradycardia, nausea, vomiting) specific to patients receiving (-)ephedrine vs etilefrine could not be distinguished. All APGAR scores were ≥8 at 5 min for both groups.

Note: Demographics and safety reported for entire treatment group population (n =60/group) not the 63-68% who met hypotension threshold definition

(Source: NDA 208289 Applicant's table page 11 of Synopses of Individual Studies)

9.4.3 Bhattarai et al. 2010

Bhattarai et al. 2010	**(Efficacy, Safety)**
Citation:	Bhattarai B, Bhat SY, Upadya M. 2010. Comparison of bolus phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anesthesia in cesarean section. J Nepal Med Assoc. 49(177):23-28.
Country:	India
Study Design:	Randomized, double-blind, controlled study
Procedure:	Elective or emergency C-section delivery
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	30 females Mean age: 24.89 ± 3.54 years Mean weight: 55.20 ± 5.33 kg
(-)**Ephedrine Dose, Administration:**	(-)Ephedrine group received 5 mg as bolus if subject developed hypotension

Comparator:	Phenylephrine (n = 30): 25 µg as bolus Mephentermine (n = 30): 6 mg as bolus
Efficacy Results:	It was found that the rise in blood pressure was significantly higher in the phenylephrine group in the first 6 minutes; after the bolus, there was significant reduction in the HR in phenylephrine group, but there was tachycardia following administration of bolus (-)ephedrine and mephenteramine.
Efficacy Conclusion:	All 3 drugs maintained hemodynamics within 20% of the baseline values on intravenous administration.
Safety Findings:	Neonatal Apgar scores were similar in all 3 groups. All groups had mean Apgar scores of more than 7 at 1 minute and of 9 at 6 minutes. One subject in the phenylephrine group complained of nausea and 3 subjects in the (-)ephedrine group complained of thumping heart.

(Source: NDA 208289 Applicant's table page 12 of Synopses of Individual Studies)

9.4.4 Ganeshanavar et al. 2011

Ganeshanavar et al. 2011	**(Efficacy, Safety)**
Citation:	Ganeshanavar A, Uday AS, Adarsh SE, Ramesh K, Ravi R. 2011. Comparison of bolus phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anaesthesia in caesarean section. J Clin Diagn Res. 5(5):948-952.
Country:	India
Study Design:	Open-label, sequential series comparison of phenylephrine, (-)ephedrine, and mephentermine
Procedure:	Elective or emergency caesarian delivery
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	30 females Mean age 22.7 ± 2.32
(-)**Ephedrine Dose, Administration:**	IV bolus of (-)ephedrine HCl, 6 mg, when there was a decrease in SBP ≥ 20% or < 90 mmHg
Comparator:	Phenylephrine, 100 mcg (n=30) Mephentermine, 6 mg (n=30)
Efficacy Results:	Increase SBP above hypotension threshold reached by all patients. Maximum mean increase in SBP after (-)ephedrine = 33.1.
Safety Findings:	Nausea and vomiting were noted but frequency or severity were not stated. Mean heart rate decreased slightly post (-)ephedrine dosing. There was no significant effect of vasopressor on fetus in terms of Apgar score at 1 and 5 minutes.

(Source: NDA 208289 Applicant's table page 14 of Synopses of Individual Studies)

9.4.5 Kansal et al. 2005

Kansal et al. 2005	**(Efficacy, Safety)**
Citation:	Kansal A, Mohta M, Sethi AK, Tyagi A, Kumar P. 2005. Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section. Anaesthesia. 60(1):28-34.
Country:	India
Study Design:	Randomized, double-blind comparison of (-)ephedrine versus mephentermine
Procedure:	Elective C-section delivery
Type of Anesthesia:	Spinal anesthesia (subarachnoid block)
(-)**Ephedrine-Treated Subjects:**	30 females ASA I, II Mean age: 26.2 ± 3.97 years Mean weight: 53.7 ± 9.28 kg
(-)**Ephedrine Dose, Administration:**	Intravenous bolus 5 mg then intravenous infusion 2.5 mg/min titrated as needed after anesthesia start for hypotension.
Comparator:	Mephentermine intravenous bolus 5 mg then intravenous infusion 2.5 mg/min titrated as needed (n = 30)
Efficacy Results:	Baseline hemodynamic parameters, hemodynamic changes subsequent to the start of vasopressor infusion, duration of hypotension, and amount of vasopressor required were statistically similar for both groups.
Efficacy Conclusion:	Mephentermine can be used as safely and effectively as (-)ephedrine for the management of hypotension.
Safety Findings:	Neonatal Apgar scores and acid-base profiles were comparable for the two groups.

(Source: NDA 208289 Applicant's table page 15 of Synopses of Individual Studies)

9.4.6 Kitchen et al. 2014

Kitchen et al. 2014	**(Efficacy, Safety)**
Citation:	Kitchen CC, Nissen P, Secher NH, Nielsen HB. 2014. Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension. Front Physiol. 5:407.
Country:	Denmark
Study Design:	Open label
Procedure:	Elective abdominal surgery
Type of Anesthesia:	General anesthesia

(-)**Ephedrine-Treated Subjects:**	9 Mean age: 67 ± 3 years Mean weight: 84 ± 18 kg
(-)**Ephedrine Dose, Administration:**	10 mg IV bolus after reduction in MAP below 60 mmHg
Comparator:	Calcium chloride (n=10): 5 mmol Phenylephrine (n=11): 0.1-0.2 mg Adrenaline (n=6): 1-2 µg Noradrenaline (n=11): 2-4 µg
Efficacy Results:	Hypotensive threshold MAP = 55 ± 3 Post-(-)ephedrine MAP = 74 ± 9 ($p < 0.05$)
Safety Findings:	No adverse events were reported. Mean cerebral oxygenation did not change post (-)ephedrine dosing. Mean cardiac output increased significantly post (-)ephedrine.

(Source: NDA 208289 Applicant's table page 17 of Synopses of Individual Studies)

9.4.7 Lecoq et al. 2010

Lecoq et al. 2010	**(Efficacy, Safety)**
Citation:	Lecoq JP, Brichant JF, Lamy ML, Joris JL. 2010. Norepinephrine and ephedrine do not counteract the increase in cutaneous microcirculation induced by spinal anaesthesia. Br J Anaesth. 105(2):214-219.
Country:	Belgium
Study Design:	Randomized, double-blind, parallel, positive controlled
Procedure:	Not specified ASA I-II
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	21 (7 males, 14 females) Mean age: 39 (22-65) years Mean weight: 65 ± 10 kg
(-)**Ephedrine Dose, Administration:**	0.2 mg/kg with a max of 10 mg IV bolus after >10% decrease in MAP. Supplementary fluid loading occurred prior to administration of treatment. Mean dose: 9.7 ± 0.3 mg
Comparator:	Norepinephrine (n=23): 0.1 mg/mL infusion at 3 mL/h until MAP returned to baseline. Supplementary fluid loading occurred prior to administration of treatment.

Efficacy Results:	Hypotension was reversed to above the threshold criteria in all patients. Baseline MAP = 93± 10 MAP Hypotension Threshold = 83± 8 Post-(-)ephedrine MAP = 95 ± 8
Safety Findings:	No adverse events were reported. Skin blood perfusion slightly increased in the area under spinal block (foot) ($p < 0.001$) and slightly decreased at the non-spinal block area (sternum) ($p < 0.01$).

(Source: NDA 208289 Applicant's table page 18 of Synopses of Individual Studies)

9.4.8 Meng et al. 2011—British Journal of Anaesthesia and Meng et al. 2011—Anesthesia Analgesia

Meng et al. 2011a, Meng et al. 2011b	**(Efficacy, Safety)**
Citation:	Meng L, Cannesson M, Alexander BS, Yu Z, Kain ZN, Cerussi AE, Tromberg BJ, Mantulin WW. 2011a. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth. 107(2):209-217. Meng L, Tran NP, Alexander BS, Laning K, Chen G, Kain ZN, Cannesson M. 2011b. The impact of phenylephrine, ephedrine, and increased preload on third-generation Vigileo-FloTrac and esophageal doppler cardiac output measurements. Anesth Analg. 113(4):751-757.
Country:	US
Study Design:	Randomized, two-way crossover
Procedure:	Elective surgery ASA I-III
Type of Anesthesia:	General anesthesia
(-)**Ephedrine-Treated Subjects:**	29 (20 males, 9 females) Mean age: 59 ± 13 years Mean weight: 77 ± 13 kg
(-)**Ephedrine Dose, Administration:**	5-20 mg IV bolus when MAP decreased >20% or MAP of <60 mmHg
Comparator:	Phenylephrine (n=29): 100-200 µg
Efficacy Results:	Hypotension was reversed to above the threshold criteria in all patients. Baseline MAP was not stated. Hypotensive threshold MAP = 53 ± 12 Post-(-)ephedrine MAP = 80 ± 13

Safety Findings:	No adverse events were reported. Cardiac output and cerebral oxygenation remained unchanged after (-)ephedrine bolus treatment.

(Source: NDA 208289 Applicant's table page 20 of Synopses of Individual Studies)

9.4.9 Nag 2010

Nag 2010	**(Efficacy, Safety)**
Citation:	Nag K. 2010. One year randomized clinical trial to compare the efficacy of intravenous bolus phenylephrine and ephedrine in maintaining arterial blood pressure during spinal anesthesia in caesarean section (Unpublished dissertation). Jawaharlal Nehru Medical College, Belgaum, Karnataka, India.
Country:	India
Study Design:	Randomized, double-blind, parallel, positive controlled
Procedure:	Caesarean delivery ASA I and II
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	6 mg IV bolus when BP ≥20% of baseline or less than 90 mmHg
(-)**Ephedrine Dose, Administration:**	50 females Mean age: 26.88 ± 1.73 years Mean weight: 55.20 ± 5.33 kg
Comparator:	Phenylephrine (n=50): 40 µg IV bolus bolus when BP ≥20% of baseline or less than 90 mmHg
Efficacy Results:	Mean number of bolus: 1.40 ± 0.64 Mean dose: 8.4 SBP in (-)ephedrine group was restored to ≥80% of baseline value. Baseline SBP = 123.14 ± 8.98 Hypotensive threshold SBP = 82.06 ± 12.81 Maximum SBP after (-)ephedrine = 109.83 ± 7.256
Safety Findings:	No adverse events were reported. MAP was considerably lower compared to phenylephrine. Mean heart rate increased post-(-)ephedrine administration. No significant effect on the APGAR score at 1 and 5 minutes was found in either group.

(Source: NDA 208289 Applicant's table page 21 of Synopses of Individual Studies)

9.4.10 Ngan Kee et al. 2001

Ngan Kee et al. 2001	**(Efficacy, Safety)**

Citation:	Ngan Kee WD, Lau TK, Khaw KS, Lee BB. 2001. Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section. Anesthesiology. 95(2):307-313.
Country:	China
Study Design:	Randomized, double-blind, parallel, positive controlled
Procedure:	Caesarean delivery ASA I and II
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	25 females* Mean age: 32 ± 3 years Mean weight: 66 ± 10 kg
(-)**Ephedrine Dose, Administration:**	When SAP decreased to less than 90% of baseline value, initial 10 mg IV bolus followed by 5 mg/min infusion until SAP increased above baseline values.
Comparator:	Metaraminol (n=25): Initial 0.5 mg IV bolus dose then 0.25 mg/min until SAP increased above baseline values
Efficacy Results:	Hypotension was reversed to above the threshold criteria in all patients. Mean baseline SAP was not reported Lowest recorded mean ±SD SAP = 96 ± 13 (range 74 – 118) Highest recorded mean ±SD SAP = 137 ± 16 (range 117 – 174)
Safety Findings:	Five patients in the (-)ephedrine group reported nausea or vomiting. Mean heart rate increased post-(-)ephedrine administration. An APGAR scored of <7 at 1 minute was reported in 1 case (4%). All APGAR scored were ≥ 7 at 5 minutes. Nine neonates (39%) had an umbilical arterial pH <7.2. (-)Ephedrine was associated with greater fetal acidosis.

*Only 23 of the patients were dosed with (-)ephedrine

(Source: NDA 208289 Applicant's table page 22 of Synopses of Individual Studies)

9.4.11 Ngan Kee et al. 2008

Ngan Kee et al. 2008b	**(Efficacy, Safety)**
Citation:	Ngan Kee WD, Shaw KS, Lau TK, Ng FF, Chui K, Ng KL. 2008b. Randomised double-blinded comparison of phenylephrine versus ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section. Anaesthesia. 63(12):1319-1326.
Country:	China
Study Design:	Randomized, double-blind comparison of (-)ephedrine versus phenylephrine

Procedure:	Nonelective C-section delivery
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	102 females Mean age: 30 ± 4.3 years Mean weight: 65.6 ± 8.6 kg
(-)**Ephedrine Dose, Administration:**	Intravenous bolus of (-)ephedrine 10 mg immediately after episode of hypotension (SBP < 100 mmHg)
Comparator:	Phenylephrine 100 µg (n = 102)
Efficacy Results:	The number of episodes of hypotension and the total volume of intravenous fluid given in each group was similar. The number of doses of vasopressor required was similar between groups.
Efficacy Conclusion:	Phenylephrine and (-)ephedrine are both suitable vasopressors for use in nonelective C-section deliveries.
Safety Findings:	The minimum recorded maternal HR was lower in the phenylephrine group versus the (-)ephedrine group, but there was no difference in maximum recorded HR or minimum and maximum recorded SBP. More subjects had nausea or vomiting in the (-)ephedrine group versus the phenylephrine group (13/102 [12.7%] vs 4/102 [3.9%], p = 0.02). Umbilical arterial and umbilical venous pH and base excess were similar between groups. In the (-)ephedrine group, umbilical arterial lactate concentration was higher (median 2.6 [IQR = 2.3-3.3] vs 2.4 [IQR = 1.9-3.0] mmol/L, p = 0.002), and umbilical venous lactate concentration was higher (2.5 [IQR = 2.2-3.2] vs 2.3 [IQR = 1.9-2.8] mmol/L, p = 0.016). Clinical neonatal outcome was similar. Of the protocol-compliant patients (n = 148), umbilical arterial Po_2 and umbilical venous Po_2 were lower in the phenylephrine group, although oxygen content was similar.

(Source: NDA 208289 Applicant's table page 23 of Synopses of Individual Studies)
Note: In this publication, 74 subjects received ephedrine, not 102.

9.4.12 Nissen et al. 2010

Nissen et al. 2010	**(Efficacy, Safety)**
Citation:	Nissen P, Brassard P, Jørgensen TB, Secher NH. 2010. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care. 12(1):17-23.
Country:	Denmark
Study Design:	Open label, sequential series

Procedure:	Elective mastectomy, thyroidectomy, or parathyroidectomy ASA I or II
Type of Anesthesia:	General anesthesia
(-)**Ephedrine-Treated Subjects:**	12 females Mean age: 53 ± 19 years Mean weight: 71 ± 16 kg
(-)**Ephedrine Dose, Administration:**	10 mg IV bolus when MAP decreased to <60 mmHg
Comparator:	Phenylephrine (n=13): 100 µg IV bolus when MAP decreased to <60 mmHg
Efficacy Results:	Hypotension was reversed to above the threshold criteria in all patients. Baseline MAP = 91 ± 18 Hypotensive threshold MAP = 53 ± 9 Maximum MAP after (-)ephedrine = 79 ± 8
Safety Findings:	No adverse events were reported. (-)Ephedrine restored CO, but had no influence on HR or total peripheral resistance or cerebral oxygenation.

(Source: NDA 208289 Applicant's table page 24 of Synopses of Individual Studies)

9.4.13 Pennekamp et al. 2011

Pennekamp et al. 2011	**(Efficacy, Safety)**
Citation:	Pennekamp CWA, Immink RV, Moll FL, Buhre WF, de Borst GJ. 2011. Differential effect of phenylephrine and ephedrine on cerebral haemodynamics before carotid cross-clamping during carotid endarterectomy. Br J Anaesth. 109(5):831-833.
Country:	The Netherlands
Study Design:	Comparative, parallel positive control design study
Procedure:	Carotid endarterectomy
Type of Anesthesia:	General anesthesia
(-)**Ephedrine-Treated Subjects:**	7
(-)**Ephedrine Dose, Administration:**	5-10 mg IV bolus when MAP decreased >20% of pre-operative values
Comparator:	Phenylephrine (n=4): 50-100 µg IV bolus when MAP decreased >20% of pre-operative values
Efficacy Results:	Hypotension was reversed to above the threshold criteria in all patients. Baseline MAP was not reported Hypotensive threshold MAP = 79 ± 12 3 minutes post-(-)ephedrine MAP = 89 ± 11

Safety Findings:	No adverse events were reported. Cerebral artery blood velocity remained constant in the (-)ephedrine group. Heart rate and frontal lobe oxygenation increased.

(Source: NDA 208289 Applicant's table page 25 of Synopses of Individual Studies)

9.4.14 Prakash et al. 2010

Prakash et al. 2010	**(Efficacy, Safety)**
Citation:	Prakash S, Pramanik V, Chellani H, Salhan S, Gogia AR. 2010. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for Caesarean delivery: A randomized study. Int J Obstet Anesth. 19(1):24-30.
Country:	India
Study Design:	Randomized, double-blind comparison of (-)ephedrine versus phenylephrine
Procedure:	Elective C-section delivery
Type of Anesthesia:	Spinal anesthesia
(-)**Ephedrine-Treated Subjects:**	30 females ASA I Mean age: 24.5 ± 4.4 years Mean weight: 56.6 ± 6.7 kg
(-)**Ephedrine Dose, Administration:**	Intravenous bolus (-)ephedrine 6 mg/mL as needed after anesthesia start for SBP ≤ 80% baseline
Comparator:	Phenylephrine 100 µg/mL (n = 30)
Efficacy Results:	Changes in systolic pressure were comparable in the 2 groups.
Efficacy Conclusion:	Phenylephrine and (-)ephedrine had similar efficacy in this study. Neonates in the phenylephrine group had significantly higher umbilical artery pH and base excess values than those in the (-)ephedrine group, which is consistent with other studies.

Safety Findings:	There were no differences in the incidence of bradycardia ((-)ephedrine: 0% vs phenylephrine: 16.7%; $p > 0.05$), nausea ((-)ephedrine: 13% vs phenylephrine: 0%; $p > 0.05$), and vomiting ((-)ephedrine: 3.3% vs phenylephrine: 0%; $p > 0.05$). Umbilical artery pH ((-)ephedrine: 7.29 ± 0.04 vs phenylephrine: 7.32 ± 0.04; $p = 0.01$) and venous pH ((-)ephedrine: 7.34 ± 0.04 vs phenylephrine: 7.38 ± 0.05; $p = 0.002$) were significantly greater in phenylephrine than in (-)ephedrine. Umbilical arterial base excess was significantly less in (-)ephedrine (-2.83 ± 0.94 mEq/L) than in phenylephrine (-1.61 ± 1.04 mEq/L; $p < 0.001$). Apgar scores at 1, 5, and 10 minute and neurobehavioral scores at 2 to 4 hours, 24 hours, and 48 hours were similar in the 2 groups ($p > 0.05$).

(Source: NDA 208289 Applicant's table page 26 of Synopses of Individual Studies)

Reference ID: 3923762

9.5 Summary of publications that support the safety of Akovaz

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Abdalla et al. 2014 (Egypt; June 2012 – June 2013) Ephedrine HCl = Eph Phenylephrine = Phe	▪ Full-term pregnant, women undergoing elective C-section delivery with preeclampsia (blood pressure ≥140/90 with proteinuria and lower limb edema) ▪ Major exclusions: Patients with pre-existing systemic disease, known fetal abnormalities, taking medications that could influence hemodynamic response	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SBP ≥25% of baseline value or SBP <90 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (20) All female 22.5 ±8.2	6 mg {4.9 mg FB} IV bolus	Heart rate increased	APGAR mean ± SD at both 1 and 5 min = 9.9 ± 0.5 Umbilical artery pH mean (interquartile range) = 7.29 (6.8 – 7.4)
					Phe (20) All female 21.4 ± 2.0	75 µg IV bolus	Heart rate decreased	All APGAR scores were 10 at 1 and 5 min post-delivery Umbilical artery pH mean (interquartile range) = 7.31 (7.08 – 7.45)

(Source: NDA 208289 Applicant's table page 66 of Integrated Summary of Safety) (Abdalla 2014)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Adigun et al. 2010 (Nigeria; Jul – Dec 2005) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Note: demographics and safety reported for entire treatment group population (n =31/group) not the 24% who met hypotension threshold definition. ▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in systolic blood pressure (SBP) ≥30% or <100 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score	Eph (7) 29.8± 3.3	Single 5 mg {4.1 mg FB} IV bolus	Nausea = 4 (12.9%) pts Hypertension = 1 (3%) Mean heart rate increased post-Eph	All APGAR scores ≥8 at 1 or 5 min
					Phe (8) 31.2± 5.7	Single 100 µg IV bolus	Nausea = 3 (10%) pts Mean heart rate decreased post-Phe	All APGAR scores ≥8 at 1 or 5 min

(Source: NDA 208289 Applicant's table page 14 of Integrated Summary of Safety) (Adigun, Amanor-Boadu, and Soyannwo 2010)

Literature Citation (Study Site Location; Dates of Study Conduct)	Patient Population	Study Design Anesthesia Used and Related Surgical Procedures	Hypotension Threshold Used for Initiation of Treatment	Safety Endpoints Reported	Treatment Groups (n) Age (mean ± SD; min, max in years)	Dose/Regimen	Safety-Related Findings	
							Maternal	Neonate
Balcan et al. 2011 (abstract only) (Romania; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Pregnant women undergoing C-section delivery ▪ ASA Grade I or II	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading	Decrease in blood pressure >20% from baseline	Maternal ▪ Heart rate ▪ Blood pressure Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Neurobehavioral scores	Eph (41) Not reported	6 mg {4.9 mg FB} IV bolus	Adverse events not reported	APGAR scores did not differ between treatment groups All umbilical artery pH values were ≥7.2 Neurobehavioral scores at 2-4h, 24 h, and 48 h post-delivery did not differ between treatment groups
					Phe (41) Not reported	100 µg IV bolus		

(Source: NDA 208289 Applicant's table page 19 of Integrated Summary of Safety) (Adigun, Amanor-Boadu, and Soyannwo 2010) Note: The ephedrine in Balcan et al. 2011 has not been confirmed to be the (-)-ephedrine enantiomer by the CMC reviewer for this submission.

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Belzarena 2006 (Brazil; dates not stated) (-)Ephedrine Sulfate = Eph Etilefrine = Eti	Note: demographics and safety reported for entire treatment group population (n =60/group) not the 63-68% who met hypotension threshold definition ▪ Pregnant women undergoing elective C-section delivery ▪ Excluded patients with hypertension	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, 20 µg fentanyl, and 100 µg morphine ▪ Pre-anesthesia IV fluid loading	Decrease in systolic blood pressure (SBP) or mean blood pressure ≥20 mmHg	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score	Eph (38) 34±5	10 mg {7.7 mg FB} IV bolus 22 (58%) received single bolus	Safety results specific to patients receiving Eph could not be distinguished	All APGAR scores ≥8 at 5 min
					Eti (41) 33±5	2 mg IV bolus 27 (66%) received single bolus	Safety results specific to patients receiving Eti could not be distinguished	All APGAR scores ≥8 at 5 min

(Source: NDA 208289 Applicant's table page 15 of Integrated Summary of Safety) (Belzarena 2006)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Berends et al. 2005 (Belgium; dates not stated) Ephedrine = Eph	▪ Singleton pregnant women scheduled for non-emergent C-section delivery with severe preeclampsia ▪ Major exclusions included patients with coagulation disorders, parturients in active labor, and twin pregnancies	Randomized ▪ Ropivacain 0.5%, sufentanil ▪ 0.5% hyperbaric bupivacaine, sufentanil ▪ Pre-anesthesia IV fluid loading (CSE-F and EA-F) or prophylactic Eph (CSE-V) ▪ Positioned with left uterine displacement	Decrease in MAP >15% of baseline value	Maternal ▪ Heart rate ▪ MAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Combined spinal epidural – fluids (CSE-F) (10) All female 29 ± 4	Bolus of lactated Ringer's solution when hypotension. If unresponsive to lactated Ringer's solution, hydroxyethylstarch was administered If unresponsive, 5 mg Eph IV bolus was given until BP was restored to normal limits or until a total dose of 50 mg was given. If hypotension persisted, 100 mcg phenylephrine was given.	HR not significantly different between groups. No episodes of tachycardia, bradycardia, or hypertension. No reports of pulmonary edema and none needed admission to the ICU. No symptoms consistent with postdural puncture headache or any other anesthetic complication reported.	No significant differences in Apgar scores, umbilical arterial and venous pH or umbilical arterial base deficit. No significant differences in the number of neonates who needed admission to the neonatal unit.
					Epidural group – fluids (EA-F) (10) All female 28 ± 7	Bolus of lactated Ringer's solution when hypotension. If unresponsive to lactated Ringer's solution, hydroxyethylstarch was administered If unresponsive, 5 mg Eph IV bolus was given until BP was restored to normal limits or until a total dose of 50 mg was given. If hypotension persisted, 100 mcg phenylephrine was given.		
					Combined spinal epidural – vasopressor (CSE-V) (10) All female 33 ± 4	5 mg Eph IV bolus was given until BP was restored to normal limits or until a total dose of 50 mg was given. If hypotension persisted, 100 mcg phenylephrine was given		

(Source: NDA 208289 Applicant's table page 68 of Integrated Summary of Safety) (Berends et al. 2005)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Bhattarai et al. 2010 (India; May 2007 – May 2008) (-)Ephedrine HCl = Eph Phenylephrine = Phe Mephentermine = Mep	▪ Singleton full-term pregnant women undergoing elective or emergency C-section delivery who met hypotension threshold definition ▪ Major exclusions: Patients with hypertension or other co-morbid diseases	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Prophylactic ranitidine and metoclopramide	Decrease in systolic blood pressure (SBP) ≥20% or <90 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score	Eph (30) 24.9± 3.5	5 mg {4.1 mg FB} IV bolus Mean ± SD number of bolus doses = 2.5 ± 0.5	Three patients reported "thumping heart" Mean heart rate increased post-Eph	All APGAR scores >7
					Phe (30) 25.2± 3.2	25 µg IV bolus Mean ± SD number of bolus doses = 3.5 ± 0.5	One patient reported nausea Mean heart rate decreased post-Phe	All APGAR scores >7
					Mep (30) 24.6± 3.4	6 mg IV bolus Mean ± SD number of bolus doses = 2.9 ± 0.4	No adverse events reported Mean heart rate increased post-Mep	All APGAR scores >7

(Source: NDA 208289 Applicant's table page 13 of Integrated Summary of Safety) (Bhattarai, Bhat, and Upadya 2010)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Clark et al. 2005 (United Kingdom; dates not stated but recruitment over 20 months) Ephedrine = Eph	▪ Pregnant, adult women undergoing elective or urgent C-section delivery with preeclampsia (diastolic blood pressure >110 mmHg stabilized with nifedipine, labetalol, or methyldopa alone or in combination) or normotensive ▪ Major exclusions: Patients with an eclamptic fit, <153 or >170 cm in height, or >100 kg in body weight	Open label, parallel, controlled ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in SBP ≥20% of baseline value or if patient exhibited symptoms (nausea or vomiting) associated with hypotension	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score	Eph (severe preeclampsia) (17) All female 30.9 ± 6.2	6 mg IV bolus repeated at 2 min intervals until threshold criteria no longer met Mean ± SD (95% CI) total dose = 16.4 ± 15.0 mg (9.3, 23.4)	Nausea = 8 pts Vomiting = 1 pt Bradycardia (<60 bpm) = 1 pt	1 neonate with APGAR score <7 at 5 min
					Eph (normotensive) (20) All female 29.7 ± 4.7	6 mg IV bolus repeated at 2 min intervals until threshold criteria no longer met Mean ± SD (95% CI) total dose = 27.9 ± 11.6 mg (22.5, 33.3)	Nausea = 12 pts Vomiting = 6 pt Bradycardia (<60 bpm) = 4 pt	All APGAR scores ≥7 at 5 min

(Source: NDA 208289 Applicant's table page 67 of Integrated Summary of Safety) (Clark, Sharwood-Smith, and Stewart 2005)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Cooper et al. 2002 (United Kingdom; dates not reported) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Singleton pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with history of preeclampsia or diabetes, or fetal abnormalities	Randomized, double-blind, parallel, positive control (stratified for the 4 different spinal anesthesia approaches used) ▪ Four different anesthetic approaches used with 0.5% hyperbaric bupivacaine or levobupivacaine, fentanyl ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease of >20% of baseline value Complex infusion algorithm with option for additional 1 -2 mL of IV bolus treatment for rescue	Maternal ▪ Heart rate ▪ SAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (50) 29 median (IQR 27-32)	3 mg/mL {2.5 mg/mL FB} initially at 20 mL/h and adjusted by 0.5 x or 2x increments to maintain SAP between ± 25% of baseline values Total dose not reported	Nausea = 30% of pts Vomiting =36% of pts	All APGAR scores were ≥9 at 1 and 5 min post-delivery 21 cases of umbilical artery pH <7.2
					Eph + Phe (49) 31 median (IQR 27-34)	Eph 1.5 mg/mL {1.2 mg/mL FB} and Phe 50 µg/mL initially at 20 mL/h and adjusted by 0.5 x or 2x increments to maintain SAP between ± 25% of baseline values Total dose not reported	Nausea = 37% of pts Vomiting =18% of pts 1 pt required glycopyrrolate for bradycardia (<45 bpm)	All APGAR scores were ≥9 at 1 and 5 min post-delivery 2 cases of umbilical artery pH <7.2
					Phe (48) 30 median (IQR 26-35)	100 µg/mL initially at 20 mL/h and adjusted by 0.5 x or 2x increments to maintain SAP between ± 25% of baseline values Total dose not reported	Nausea = 17% of pts Vomiting = 0 pts 1 pt required glycopyrrolate for bradycardia (<45 bpm)	All APGAR scores were ≥9 at 1 and 5 min post-delivery 2 cases of umbilical artery pH <7.2

(Source: NDA 208289 Applicant's table page 45 of Integrated Summary of Safety) (Cooper et al. 2002)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Cooper et al. 2007 (United Kingdom; dates not reported) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with history of preeclampsia or diabetes, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, diamorphine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic metoclopramide and glycopyrrolate	SAP decreases ≥20% of baseline could be treated with 1 mL of assigned drug if at max infusion rate	Maternal ▪ Heart rate ▪ SAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (27) 29 (21 – 41)	4.5 mg/mL {3.7 mg/mL FB} at 20 mL/h with infusion rate double or halved to maintain SAP at baseline values with max rate allowed of 40 mL/h and min rate allowed of 2.5 mL/h Median (IQR) total dose for 0 to 15 min post-anesthesia = 34 (25 -51) mg, {27.9 (20.5 – 41.8) mg FB} Median (IQR) total dose for 15 to 30 min post-anesthesia = 9 (7 -23) mg, {7.4 (5.7 – 18.9) mg FB}	Reactive hypertension 0 – 15 min post-anesthesia admin = 33% of pts Reactive hypertension 15 – 30 min post-anesthesia admin = 59% of pts Increased mean heart rate	All APGAR scores ≥9 at 1 min and 5 min post-delivery 3 cases of umbilical artery pH <7.00
					Phe (27) 30 (20 – 39)	100 µg/mL at 20 mL/h with infusion rate double or halved to maintain SAP at baseline values with max rate allowed of 40 mL/h and min rate allowed of 2.5 mL/h Median (IQR) total dose for 0 to 15 min post-anesthesia = 800 (610 -1020) µg Median (IQR) total dose for 15 to 30 min post-anesthesia = 630 (430 -960) µg	Reactive hypertension 0 – 15 min post-anesthesia admin = 35% of pts Reactive hypertension 15 – 30 min post-anesthesia admin = 24% of pts Decreased mean heart rate	All APGAR scores ≥9 at 1 min and 5 min post-delivery Lowest umbilical artery pH = 7.19

(Source: NDA 208289 Applicant's table page 43 of Integrated Summary of Safety) (Cooper et al. 2007)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Critchley et al. 1995 (China [Hong Kong]; dates not stated) Ephedrine = Eph	▪ Patients >60 years undergoing surgical fixation of fractured neck of femur ▪ ASA Grade II or III ▪ Major exclusions: Patients with diabetes, severe	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Premedication with diazepam	Decrease in SAP >25% of baseline	▪ Heart rate ▪ Systolic and mean arterial pressure ▪ Central venous pressure	Eph – bolus then infusion (started immediately after anesthesia administration) then Eph rescue bolus if threshold met (15) 3M/12F 79 (65 – 93)	0.2 mg/kg initial IV bolus then 0.5 mg/kg/h infusion Mean total dose = 28 (19 – 43) mg	Not reported	Heart rate increased
					Eph – bolus then infusion + colloid (started immediately after anesthesia administration) then Eph rescue bolus if threshold met (15) 6M/9F 74 (60 – 89)	0.2 mg/kg IV bolus then 0.5 mg/kg/h infusion Mean total dose = 23 (16 – 35 mg)	Not reported	Heart rate increased

(Source: NDA 208289 Applicant's table page 72 of Integrated Summary of Safety) (Critchley et al. 1995)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Damevski et al. 2011 (Republic of Macedonia; dates not reported) (-)Ephedrine HCl = Eph	■ Singleton, full-term pregnant women undergoing elective C-section delivery ■ ASA Grade I ■ Major exclusions: Patients with body weight > 90 kg	Randomized, parallel, controlled ■ 0.5% hyperbaric bupivacaine, fentanyl ■ Positioned with left uterine displacement	Decrease in SAP <100 mmHg	Maternal ■ Heart rate ■ SAP Neonate ■ APGAR score	Pre-hydration Ringer's solution control (20) 23.6 ± 2.4	Please see Table 2 for data.		
					Eph (20) 24.3 ± 2.8	No prehydration; 0.1 mg/mL {0.082 mg/mL FB} Eph continuous infusion with Eph 5 mg {4.1 mg FB} IV bolus rescue doses when hypotension definition met Mean (± SD) total dose = 30 (4.1) mg, {24.6 (3.4) mg FB}	Nausea = 8 pts (40%) Vomiting = 6 pts (30%)	All APGAR scores ≥9 immediately post delivery

(Source: NDA 208289 Applicant's table 5 page 49 of Integrated Summary of Safety) (Damevski et al. 2011)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Damevski et al. 2011 (Republic of Macedonia; dates not reported) (-)Ephedrine HCl = Eph	▪ Pregnant women undergoing elective C-section delivery ▪ ASA Grade I ▪ Major exclusions: Patients with body weight > 90 kg	Randomized, parallel, controlled ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Positioned with left uterine displacement	Decrease in SAP <100 mmHg	Maternal ▪ Heart rate ▪ SAP Neonate ▪ APGAR score	Pre-hydration Ringer's solution control (20) 23.6 ± 2.4	Eph 10 mg {8.2 mg FB} IV bolus rescue doses when hypotension definition met Mean (± SD) total dose = 25 (2) mg {20.5 (1.6) mg FB}	Nausea = 12 pts (60%) Vomiting = 10 pts (50%)	All APGAR scores ≥9 immediately post delivery
					Eph (20) 24.3 ± 2.8	Please see Table 5 for data.		

(Source: NDA 208289 Applicant's table 2 page 22 of Integrated Summary of Safety) (Damevski et al. 2011; Desalu and Kushimo 2005) Note: The ephedrine used in Damevski et al. 2011 has not been confirmed to be the (-)-ephedrine enantiomer per the CMC reviewer of this submission.

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Datta et al. 1982 (US; dates not stated) Ephedrine = Eph	Pregnant, adult women undergoing elective C-section delivery	Open-label semi-sequential ▪ 0.5% tetracaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SBP >30 mmHg from baseline or <100 mmHg	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph –SBP threshold drop (18) All female Not reported	10 mg IV bolus (multiple as needed)	Frequency of nausea and/or vomiting = 66%	Percentage of neonates with APGAR scores at 1 min <7 = 83% but 0 at 5 min Umbilical artery pH mean ± SE = 7.23 ± 0.01
					Eph –any drop in SBP (20) All female Not reported	10 – 30 mg IV bolus	Frequency of nausea and/or vomiting = 10%	All APGAR scores ≥7 at 1 or 5 min Umbilical artery pH mean ± SE = 7.3 ± 0.01
					Untreated – no drop in SPB (22) All female Not reported	Not applicable	Frequency of nausea and/or vomiting = 0	All APGAR scores ≥7 at 1 or 5 min Umbilical artery pH mean ± SE = 7.3 ± 0.01

(Source: NDA 208289 Applicant's table page 60 of Integrated Summary of Safety) (Datta et al. 1982)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Defossez et al. 2007 (abstract only) (Belgium; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Pregnant women undergoing C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, epilepsy, psychiatric illness, or age >40 years	Randomized, double-blind, positive control Not reported	Decrease in MAP >25% of baseline or <70 mmHg	Maternal ▪ Heart rate ▪ MAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph bolus (10) Not reported	5 mg {4.1 mg FB} IV bolus Mean ± SD total dose = 31 ± 14.2 mg {25.4 ± 11.6 mg FB}	Specific data not reported but stated that there were no significant differences in any safety-related endpoint between groups	
					Phe bolus (10) Not reported	100 µg IV bolus Mean ± SD total dose = 520 ± 379 µg		
					Phe continuous infusion (started immediately following establishment of anesthesia until delivery) (10) Not reported	20 µg/min Mean ± SD total dose = 1146 ± 202 µg		
					Eph continuous infusion (started immediately following establishment of anesthesia until delivery) (10) Not reported	Please see Table 5 for data.		

(Source: NDA 208289 Applicant's table 1 page 20 of Integrated Summary of Safety) (Defossez 2007)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Defossez et al. 2007 Abstract (Belgium; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Pregnant women undergoing C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, epilepsy, psychiatric illness, or age > 40 years	Randomized, double-blind, positive control Not reported	Decrease in MAP >25% of baseline or <70 mmHg	Maternal ▪ Heart rate ▪ MAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph bolus (10) Not reported	Please see Table 1 for data.		
					Phe bolus (10) Not reported	100 µg IV bolus Mean ± SD total dose = 520 ± 379 µg	Specific data not reported but stated that there were no significant differences in any safety-related endpoint between groups	
					Phe continuous infusion (started immediately following establishment of anesthesia until delivery) (10) Not reported	20 µg/min Mean ± SD total dose = 1146 ± 202 µg		
					Eph continuous infusion (started immediately following establishment of anesthesia until delivery) (10) Not reported	1 mg/min {0.82 mg/min FB} Mean ± SD total dose = 55 ± 11.7 mg, {45.1 ± 9.6 mg FB}		

(Source: NDA 208289 Applicant's table 5 page 50 of Integrated Summary of Safety) (Defossez 2007)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Desalu and Kushimo 2005 (Nigeria; dates not reported) (-)Ephedrine HCl = Eph	▪ Pregnant women undergoing elective C-section delivery ▪ Major exclusions: Patients with hypersensitivity to bupivacaine	Randomized, controlled, parallel ▪ 0.5% hyperbaric bupivacaine ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine and metoclopramide	Moderate hypotension =SBP decrease >20% of baseline Severe hypotension = decrease >30% of baseline	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score	Prehydration (30) 31.2 ± 4.1	Moderate hypotension treated with hydration. Moderate hypotension not responsive to hydration or severe hypotension treated with 3 mg {2.5 mg FB} IV bolus doses of Eph Mean (± SD) total dose of Eph = 9.8 (5.5) mg {8.0 (4.5) mg FB}	Moderate hypotension = 8 pts (27%) Severe hypotension = 12 pts (40%)	All APGAR scores ≥8 at 5 min post delivery
					Eph (30) 30.2 ± 3.0	Please see Table 5 for data.		

(Source: NDA 208289 Applicant's table 2 page 22 of Integrated Summary of Safety; modified by clinical reviewer) (Damevski et al. 2011; Desalu and Kushimo 2005)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Desalu and Kushimo 2005 (Nigeria; dates not reported) (-)Ephedrine HCl = Eph	▪ Pregnant women undergoing elective C-section delivery ▪ Major exclusions: Patients with hypersensitivity to bupivacaine	Randomized, double-blind, controlled, parallel ▪ 0.5% hyperbaric bupivacaine ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine and metoclopramide	Moderate hypotension =SBP decrease >20% of baseline Severe hypotension = decrease >30% of baseline	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score	Prehydration (30) 31.2 ± 4.1	Please see Table 2 for data.		
					Eph (30) 30.2 ± 3.0	0.03 mg/mL {0.025 mg/mL FB} Eph at 1.5 mg/min {1.23 mg/min FB} infusion titrated to keep SBP >100 mmHg Moderate hypotension treated with hydration. Moderate hypotension not responsive to hydration or severe hypotension treated with 3 mg {2.5 mg FB} IV bolus doses of Eph Mean (± SD) total dose of Eph = 39.8 (6.0) mg, {32.6 (4.9) mg FB}	Moderate hypotension = 9 pts (30%) Severe hypotension = 4 pts (13%)	All APGAR scores ≥8 at 5 min post delivery

(Source: NDA 208289 Applicant's table 5 page 51 of Integrated Summary of Safety) (Desalu and Kushimo 2005)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Dhungana et al. 2008 (Nepal; dates not stated) (-)Ephedrine HCl = Eph	▪ Adult patients undergoing routine surgery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, cardiovascular, cerebrovascular, respiratory, hepatic, or renal disease, morbid obesity, pregnancy, or any hypovolemic condition	Open label, randomized, controlled Induction = 2.5 mg/kg propofol Study period only 5 min after induction but before any maintenance anesthesia used	Decrease in SBP >20%	• Heart rate • Systolic, diastolic, mean arterial blood pressure	Eph (40) (9M/31F) 35.2 ± 11.1	IV bolus 0.2 mg/kg {0.16 mg/kg FB} given before anesthesia induction	Not reported	Hypotension threshold reached = 9 pts (23%)
					Colloid (39) (9M/30F) 36.8 ± 10.2	Haemaccel® (10 mL/kg)		Hypotension threshold reached = 9 pts (23%)
					No treatment (40) (11M/29F) 34.3 ± 11.1	Not applicable		Hypotension threshold reached = 27 pts (68%)

(Source: NDA 208289 Applicant's table page 54 of Integrated Summary of Safety) (Dhungana et al. 2008)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Dolci et al. 2011 (Switzerland; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Adult patients scheduled for elective surgery (type of surgery not specified) under spinal anesthesia ▪ ASA Grade I or II ▪ Major exclusions: Patients with diabetes, cardiac or neurologic disease, autonomic dysfunction, treatment with beta-blocking or vasoconstricting agents, or pregnant	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Premedication with midazolam	Decrease in mean arterial pressure (MAP) >10%	• Heart rate • MAP • Skin blood flow (SBF)	Eph (10) 6M/4F 38± 14	7.5 mg {6.2 mg FB} IV bolus (single)	Not reported	Small decrease in SBF in both lower limb (under spinal block) and upper limb (not under spinal block) post-Eph
					Phe (10) 8M/2F 45± 15	75 µg IV bolus (single)	Not reported	Increase in SBF in both lower limb (under spinal block) and upper limb (not under spinal block) post-Phe

(Source: NDA 208289 Applicant's table page 28 of Integrated Summary of Safety) (Dolci et al. 2011)
Note: The ephedrine used in Dolci et al. 2011 has not been confirmed to be the (-)ephedrine enantiomer per the CMC reviewer of this submission.

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Dyer et al. 2009 (South Africa; Nov 2007 – Mar 2008) Ephedrine Sulfate = Eph Phenylephrine = Phe	▪ Singleton, pregnant, adult women undergoing elective C-section delivery ▪ Major exclusions: Patients with cardiac, respiratory, or renal disease, anemia, preeclampsia, BMI >35, age >40 years	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, 10 µg fentanyl ▪ IV fluid loading ▪ Positioned with left uterine displace-ment	Decrease in MAP >20% of baseline value	Maternal ▪ Heart rate ▪ MAP ▪ Cardiac output (CO) ▪ Stroke volume Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (18) All female 26.4 ±4.1	10 mg {7.7 mg FB} IV bolus Mean total dose pre-delivery = 22.2 mg (range 10 – 40 mg), {17.1 (range 7.7 – 30.8) mg FB} Mean total dose post-delivery = 21.7 mg (range 10 – 50 mg), {16.7 (7.7 – 38.5) mg FB}	4 patients reported nausea and vomiting Increase from baseline in the following (mean percent ± SD): parameters: Heart rate = 7 (14.8)% Stroke volume = 5.7 (12.6)% CO (LiDCO) = 16.0 (19.5)	All APGAR scores ≥7at 1 min All APGAR scores ≥9 at 5 min Umbilical artery pH mean ± SD = 7.28 ± 0.06
					Phe (20) All female 27.1 ± 3.7	80 µg IV bolus Mean total dose pre-delivery = 167 µg (range 80 – 240 µg) Mean total dose post-delivery = 266 µg (range 80 – 800 µg)	2 patients reported nausea and vomiting Decrease from baseline in the following (mean percent ± SD): parameters: Heart rate = 25.5 (9.8)% CO (LiDCO) = 27.8 (10.7) Stroke volume minimal mean percent increase from baseline = 0.1 (17.7)%	APGAR scores between 6 and 9 at 1 min All APGAR scores ≥9 at 5 min Umbilical artery pH mean ± SD = 7.31 ± 0.04

(Source: NDA 208289 Applicant's table page 57 of Integrated Summary of Safety)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Foss et al. 2014 (Denmark; Apr 2012 – Jul 2012) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Singleton pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with history of preeclampsia, elevated serum bilirubin or HELLP-syndrome (hemolysis, elevated liver enzyme, low platelet count)	Open label, balanced randomization, parallel ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	SBP decrease of 10 – 20% of baseline values IV bolus doses of treatment allowed if SBP decreased to >20% of baseline or if patient symptomatic	Maternal ▪ Heart rate ▪ SBP ▪ DBP ▪ MAP ▪ Frontal lobe oxygenation (ScO_2) Neonate ▪ Heart rate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (12) 30.8 ± 5.5	5 mg/mL {4.1 mg/mL FB} initially at 20 mL/h and adjusted by 0.5 x or 2x increments to maintain SBP between ± 20% of baseline values Total dose of Eph not reported	Frontal lobe oxygenation unchanged from baseline	All APGAR scores were 8 at 1 min and 10 at 5 min post-delivery Mean (± SD) umbilical artery pH = 7.29 (0.08) Mean fetal heart rate increased from baseline
					Phe (12) 33.0 ± 3.7	100 µg/mL initially at 20 mL/h and adjusted by 0.5 x or 2x increments to maintain SBP between ±20% of baseline values Total dose of Phe not reported	Mean (±SE) percent frontal lobe oxygenation reduced from baseline by 8.6 (2.8) Decreased mean heart rate	All APGAR scores were 8 at 1 min and 10 at 5 min post-delivery Mean (± SD) umbilical artery pH = 7.31 (0.05) Mean fetal heart rate increased from baseline

(Source: NDA 208289 Applicant's table page 44 of Integrated Summary of Safety) (Foss et al. 2014)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ganeshanavar et al 2011 (India; Nov 2010 – Aug 2011) (-)Ephedrine HC1 = Eph Phenylephrine = Phe Mephentermine = Mep	▪ Singleton full-term pregnant women undergoing elective or emergency C-section delivery who met hypotension threshold definition ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, or cardiac disease, obstetrical complications, or weighed >70 kg	Open label, sequential series ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Prophylactic ranitidine and metoclopra-mide	Decrease in systolic blood pressure (SBP) ≥20% or <90 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ Diastolic blood pressure (DBP) Neonate - none reported	Eph (30) 22.7± 2.3	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}	Nausea or vomiting noted but frequency or severity not stated Meant heart rate decreased slightly post-Eph dosing	Not reported
					Phe (30) 23.2± 2.5	100 µg IV bolus # bolus, (patient %) Single, 77% Two, 17% Three, 6% Mean ± SD total dose = 130 (50) µg	Nausea or vomiting noted but frequency or severity not stated Mean heart rate decreased markedly post-Phe dosing	Not reported
					Mep (30) 22.5±1.6	6 mg IV bolus # bolus, (patient %) Single, 47% Two, 43% Three, 10% Mean ± SD total dose = 9.8 (4.0) mg	Nausea or vomiting noted but frequency or severity not stated Mean heart rate decreased slightly post-Mep dosing	Not reported

(Source: NDA 208289 Applicant's table page 12 of Integrated Summary of Safety) (Ganeshanavar A 2011)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Gunda et al. 2010 (India; 2007 – 2008) Ephedrine = Eph Phenylephrine =Phe	▪ Pregnant, adult women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, epilepsy, pulmonary tuberculosis, bronchial asthma, and bleeding disorders	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine and metoclopramide	Decrease in SBP >30% of baseline value	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate • APGAR score	Eph (50) All female 24.1 ± 3.7	5 mg IV bolus 1 bolus = 92% of pts 2 boluses = 8% of pts	The following frequency of adverse events was reported: Nausea = 9 (18%) Vomiting = 7 (14%) Bradycardia (<60 bpm) = 1 (2%) – atropine not required Tachycardia (heart rate >30% increase from baseline) = 8 (16%)	All APGAR scores between 8-9 at 1 min and 10 at 5 min
					Phe (50) All female 23.4 ± 3.5	100 µg IV bolus 1 bolus = 94% of pts 2 boluses = 6% of pts	The following frequency of adverse events was reported: Nausea = 4 (8%) Vomiting = 0 Bradycardia (<60 bpm) = 6 (12%) – atropine treatment required Tachycardia (heart rate >30% increase from baseline) = 0	All APGAR scores between 8-9 at 1 min and 10 at 5 min

(Source: NDA 208289 Applicant's table page 56 of Integrated Summary of Safety) (Gunda et al. 2010)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Iqbal et al. 2010 (Pakistan; Jan 2008 – Jun 2008) (-)Ephedrine Sulfate = Eph	▪ Women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, or preexisting cardiac or pulmonary diseases	Randomized, double-blind, parallel, dose response ▪ 0.75% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in systolic blood pressure (SBP) ≥20% from baseline	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score	Eph 10 mg (30) 27.2± 4.4	10 mg {7.7 mg FB} IV bolus immediately after receiving spinal anesthesia If pts subsequently met hypotension threshold, given additional 10 mg {7.7 mg FB} IV bolus rescue doses of Eph and IV crystalloid solutions until SBP above threshold 14 pts (47%): no rescue (total Eph = 10 mg {7.7 mg FB}) 2 pts (7%): 10 mg rescue (total Eph = 20 mg {15.4 mg FB}) 11 pts (37%): 20 mg rescue (total Eph = 30 mg {23.1 mg FB}) 3 pts (10%): 30 mg rescue (total Eph = 40 mg {30.8 mg FB})	Nausea = 12 pts (40%) Vomiting = 3 pts (10%) 16 pts (53%) required rescue Eph No reports of reactive hypertension	2 cases (7%) of APGAR scores <7 at 1 min and 1 case <8 at 5 min post-delivery
					Eph 15 mg (30) 28.4 ± 4.1	15 mg {11.6 mg FB} IV bolus immediately after receiving spinal anesthesia If pts subsequently met hypotension threshold, given additional 10 mg {7.7 mg FB} IV bolus rescue doses of Eph and IV crystalloid solutions until SBP above threshold 26 pts (87%): no rescue (total Eph = 15 mg {11.6 mg FB}) 4 pts (13%): 10 mg rescue (total Eph = 25 mg {19.3 mg FB})	Nausea = 2 pts (7%) 4 pts (13%) required rescue Eph Reactive hypertension (SBP >20% of baseline value) = 4 pts (13%)	2 cases (7%) of APGAR scores <7 at 1 min and 0 cases at 5 min post-delivery
					Eph 20 mg (30) 26.7 ± 4.0	20 mg {15.4 mg FB} IV bolus immediately after receiving spinal anesthesia If pts subsequently met hypotension threshold, given additional 10 mg {7.7 mg FB} IV bolus rescue doses of Eph and IV crystalloid solutions until SBP above threshold 29 pts (97%): no rescue (total Eph = 20 mg {15.4 mg FB}) 1 pt (3%): 10 mg rescue (total Eph = 30 mg {23.1 mg FB})	1 pt (3%) required rescue Eph Reactive hypertension (SBP >20% of baseline value) = 14 pts (47%)	1 case (3%) of APGAR scores <7 at 1 min and 0 cases at 5 min post-delivery

(Source: NDA 208289 Applicant's table page 38 of Integrated Summary of Safety) (Iqbal and Khan 2010)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Ishiyama et al. 2003b (Japan; dates not stated) Ephedrine = Eph Phenylephrine = Phe	▪ Adult patients undergoing elective surgery under combined epidural and general anesthesia ▪ ASA Grade I or II ▪ Major exclusions: Patients neurological or psychiatric disorders, cerebral infarction, or history of alcohol or drug abuse	Randomized, parallel, controlled ▪ Epidural: 0.75% ropivacaine ▪ General anesthesia induction: 2 mg/kg propofol, sevoflurane 5% and 0.15 mg/kg vecuronium ▪ Maintenance: 0.75% sevoflurane Premedication with midazolam	Decrease in blood pressure >30% of baseline	▪ Heart rate ▪ Mean blood pressure ▪ Oxygen saturation ▪ Bispectral Index (BIS) ▪ $P_{ET}CO_2$	Eph (17) 10M/7F 61 ± 14	0.1 mg/kg IV bolus	Not reported	Slight increase in heart rate 7 patients had BIS values >60 and required increased sevoflurane concentration (1 – 1.5%)
					Phe (17) 7M/10F 63 ± 14	2 µg/kg IV bolus	Not reported	Decrease in heart rate No patient had a BIS >60
					Untreated – blood pressure did not reach threshold (9) 5M/4F 67 ± 3	Not applicable	Not reported	Decrease in heart rate No patient had a BIS >60

(Source: NDA 208289 Applicant's table page 76 of Integrated Summary of Safety) (Ishiyama et al. 2003)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	Patient Population	Study Design Anesthesia Used and Related Surgical Procedures	Hypotension Threshold Used for Initiation of Treatment	Safety Endpoints Reported	Treatment Groups (n) Age (mean ± SD; min, max in years)	Dose/Regimen	Safety-Related Findings	
							Maternal	Neonate
Kansal et al. 2005 (India; dates not stated) (-)Ephedrine HC1 = Eph Mephentermine = Mep	▪ Singleton pregnant women undergoing elective C-section delivery who met hypotension threshold definition ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, cardiac or cerebrovascular disease, autonomic neuropathy, obstetric complications, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in systolic blood pressure (SBP) ≥20% or <100 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (30) 26.2± 4.0	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}	Freq of AEs: n (%) Nausea and vomiting 5 (17%) R-R variability 1(3%) Ventricular ectopics 1 (3%) Bradycardia 1 (3%) Dizziness 1 (3%) Restlessness 1 (3%) No AEs required treatment	APGAR scores between 6 and 9 at 1 min All APGAR scores ≥8 at 5 min Umbilical arterial pH <7.2 for 3 (10%) fetuses
					Mep (30) 26.0 ± 3.3	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	Freq of AEs: n (%) Nausea and vomiting 2 (7%) Precordial pain 2 (7%) R-R variability 3 (10%) Ventricular ectopics 1 (3%) Bradycardia 2 (7%) Dizziness 2 (7%) Headache 1 (3%) Only 1 patient with bradycardia required treatment (atropine)	APGAR scores between 6 and 9 at 1 min All APGAR scores ≥7 at 1 or 5 min Umbilical arterial pH <7.2 for 5 (17%) fetus

(Source: NDA 208289 Applicant's table page 16 of Integrated Summary of Safety) (Kansal et al. 2005)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Kasaba et al. 2000[a] (Japan; dates not stated) (-)Ephedrine Hydrochloride = Eph Dopamine = Dop Dobutamine = Dob	■ Adult patients undergoing lobectomy or mastectomy ■ ASA Grade I or II Major exclusions: Patients hypertension, diabetes, or undergoing anticoagulant therapy	Randomized, parallel, controlled ■ Epidural: 2% mepivacaine ■ General anesthesia induction: 2 mg/kg propofol and 0.15 mg/kg vecuronium ■ Maintenance: 4 mg/kg/min propofol infusion ■ Pre-anesthesia IV fluid loading ■ Premedication with benzodiazepine	Decrease in MAP>10% from baseline	↓ Heart rate ↓ MAP	Eph (9) Note: 10 patients included in group but 1 did not require Eph 4 M/6F 54 (10)	5 mg {4.1 mg FB}IV bolus 1 bolus only = 5 pts 2 bolus = 3 pts 3 bolus = 1 pt	Not reported	Heart rate increased to above baseline levels after tracheal intubation
					Dop (10) 5M/5F 58 (13)	5 µg/kg/min infusion starting 5 minutes after epidural injection to end of tracheal intubation then given as needed	Not reported	
					Dob (10) 5M/5F 52 (14)	3 µg/kg/min infusion starting 5 minutes after epidural injection to end of tracheal intubation then given as needed	Not reported	
					Untreated (10) 5M/5F 59 (14)	Not applicable	Not reported	Heart rate returned to baseline levels after tracheal intubation

[a] This study used combined general and epidural anesthesia

(Source: NDA 208289 Applicant's table page 35 of Integrated Summary of Safety) (Kasaba et al. 2000) Note: The ephedrine used in Kasaba et al. 2000 has not been confirmed to be the (-)ephedrine enantiomer per the CMC reviewer of this submission.

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/ Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Kitchen et al. 2014 (Denmark; dates not reported) (-)Ephedrine HCl = Eph Adrenaline = Adr Phenylephrine = Phe Noradrenaline = Norad Calcium chloride = Cal	■ Adult patients undergoing elective major abdominal surgery who met hypotension threshold definition (28M/19F enrolled overall) ■ Major exclusions: Patients with diabetes requiring insulin and use of anti-hypertensive medications	Open label ■ Induction = 2 mg/kg propofol ■ Maintenance = 80 µg/kg/min propofol, 0.3 - 0.4 µg/kg/min remifentanil	Decrease in MAP to <60 mmHg	• Heart rate • MAP • Cardiac output • Cerebral oxygenation	Eph (9) 67 ± 3[a] Overall gender ratio: 28M/19F	10 mg {8.2 mg FB} IV bolus	Not reported	Mean cardiac output increased post-Eph Mean cerebral oxygenation did not change post-Eph
					Adr (6) 56 ± 11[a] Overall gender ratio: 28M/19F	1 -2 µg IV bolus		Mean cardiac output increased post-Adr Mean cerebral oxygenation did not change post-Adr
					Phe (11) 64 ± 7[a] Overall gender ratio: 28M/19F	100 – 200 µg IV bolus		Mean cardiac output did not change post-Phe Mean cerebral oxygenation decreased slightly post-Phe
					Norad (11) 64 ± 3[a] Overall gender ratio: 28M/19F	2 – 4 µg IV bolus		Mean cardiac output did not change post-Norad Mean cerebral oxygenation decreased slightly post-Norad
					Cal (10) Overall gender ratio: 28M/19F 60 ± 9[a]	5 mmol IV bolus		Mean cardiac output did not change post-Cal Mean cerebral oxygenation did not change post-Cal

(Source: NDA 208289 Applicant's table page 33 of Integrated Summary of Safety) (Kitchen et al. 2014)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Lecoq et al. 2010 (Belgium; dates not stated) (-)Ephedrine HCl = Eph Norepinephrine = Nor	▪ Adult patients undergoing surgery (type of surgery not specified) under spinal anesthesia ▪ ASA Grade I or II ▪ Major exclusions: Patients with diabetes, hypertension, use of cardiovascular medications, arterial disease, or morbidly obese	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, sufentanil 1.5 µg ▪ Pre-anesthesia IV fluid loading ▪ Premedication with oral alprazolam	Decrease in mean arterial pressure (MAP) >10% (after stabilization to approx. 10% below baseline levels with supplementary fluid loading)	• Heart rate • MAP • Skin blood perfusion	Eph (21) 7M/14F 39 (range 22 – 65)	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}	Not reported	Skin blood perfusion slightly increased in the area under spinal block (foot) and slightly decreased at the non-spinal block area (sternum)
					Nor (23) 8M/15F 42 (19 – 65)	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	Not reported	

(Source: NDA 208289 Applicant's table page 29 of Integrated Summary of Safety) (Lecoq et al. 2010)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Magalhaes et al. 2009 (Brazil; dates not reported) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, preexisting cardiovascular or cerebrovascular diseases, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, sufentanil ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in systolic blood pressure (SBP) ≥20% from baseline	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (30) 27.2 ± 4.5	10 mg {7.7 mg FB} IV bolus immediately after receiving spinal anesthesia If pts subsequently met hypotension threshold, given additional 5 mg IV bolus rescue doses of Eph until SBP above threshold Mean total dose of Eph = 14 mg {10.8 mg FB}	Nausea episodes = 7 Vomiting episodes = 4 Hypotension = 21 pts (70%) with total of 29 episodes Reactive hypertension episodes = 5	No APGAR scores of <7 at 1 or 5 min post-delivery Mean (± SD) umbilical arterial pH = 7.22 (0.03)
					Phe (30) 26.5 ± 5.1	80 µg IV bolus immediately after receiving spinal anesthesia If pts subsequently met hypotension threshold, given additional 40 µg IV bolus rescue doses of phenylephrine until SBP above threshold Mean total dose of phenylephrine = 186 µg	Nausea episodes = 10 Vomiting episodes = 6 Hypotension = 28 pts (93%) with total of 80 episodes Reactive hypertension episodes = 4 1 pt had bradycardia (<50 bpm) requiring atropine treatment	No APGAR scores of <7 at 1 or 5 min post-delivery Mean (± SD) umbilical arterial pH = 7.27 (0.06)

(Source: NDA 208289 Applicant's table page 39 of Integrated Summary of Safety) (Magalhaes et al. 2009)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Meersschaert et al. 2002 (France; dates not stated) (-)Ephedrine HCl = Eph Terlipressin = Ter	■ Adult patients undergoing vascular surgery and chronically treated with angiotensin converting enzyme inhibitors (ACEIs) and meeting hypotension threshold criteria after anesthesia ■ Major exclusions: Patients requiring emergency surgery, chronic treatment with ACEI for cardiac failure, chronic treatment with angiotensin II receptor inhibitor	Randomized, double—blind 2-way crossover Demographics slightly altered due to 2 patients not fully completing crossover ■ Induction = target conc propofol of 3 µg/mL and 0.5 µg/kg sufentanil, 0.5 mg/kg atracurium ■ Maintenance = target conc of 1.6 µg/mL propofol, ■ Premedication with midazolam and usual cardiac meds except ACEI	Decrease in MAP >30% of baseline or <65 mmHg	■ Heart rate ■ MAP	Eph (21) Gender not reported 66 ± 2	3 mg {2.5 mg FB} IV bolus Eph If MAP was not restored in 1 min, another bolus was given. If MAP not restored (or if third episode of hypotension occured) cross-over treatment was intiated. Median (95% CI) total dose = 6 (6 – 9) mg {4.9 (4.9 – 7.4) mg FB}	Not reported	Very slight decrease in mean heart rate values after first bolus
					Eph + Ter (19) Gender not reported 69 ± 7	3 mg {2.5 mg FB} IV bolus Eph and Ter 1 mg IV bolus If MAP was not restored in 1 min, another bolus was given. If MAP not restored (or if third episode of hypotension occured) cross-over treatment was intiated. Median (95% CI) total dose of Eph = 3 (3 – 6) mg {2.5 (2.5 – 4.9) mg FB}	Not reported	More pronounced decrease in mean heart rate values after first bolus

(Source: NDA 208289 Applicant's table page 36 of Integrated Summary of Safety) (Meersschaert et al. 2002)
Note: The ephedrine used in Meersschaert et al. 2002 has not been confirmed to be the (-)ephedrine enantiomer per the CMC reviewer of this submission.

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Meng et al. 2011a and Meng et al. 2011b (US; dates not stated) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	■ Adult patients undergoing elective surgery who met hypotension threshold definition ■ ASA Grade I, II, or III ■ Major exclusions: Patients with poorly controlled hypertension or diabetes, symptomatic cardiovascular disease, or cerebrovascular disease	Randomized, two-way crossover Mean ± SD interval between treatments = 20 ± 14 min ■ Induction = 1.5 – 2 µg/kg fentanyl, 2 – 3 mg/kg propofol ■ Maintenance = 100 – 150 µg/kg/min propofol, 0.3 - 0.5 µg/kg/min remifentanil	Decrease in mean arterial pressure (MAP) >20% or a MAP to <60 mmHg	• Heart rate • MAP • Cardiac output • Cerebral oxygenation	Eph (29) Note: 1 additional patient received Eph only but not included in reported analysis 20 M/9 F 59 ± 13 (33 – 81)	5 – 20 mg {3.85 – 15.4 mg FB} IV bolus (single)	Not reported	Cardiac output and cerebral oxygenation unchanged after Eph treatment
					Phe (29) 20 M/9 F 59 ± 13 (33 – 81)	100 – 200 µg IV bolus (single)	Not reported	Cardiac output and cerebral oxygenation decreased after Phe treatment

(Source: NDA 208289 Applicant's table page 31 of Integrated Summary of Safety) (Meng, Cannesson, et al. 2011; Meng, Tran, et al. 2011)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Mokhtar and Sherif 2014 (Egypt; dates not stated) Ephedrine = Eph Phenylephrine = Phe	▪ Full-term pregnant, adult women undergoing C-section delivery with mild preeclampsia (blood pressure ≥140/90 mmHg but <160/100 with proteinuria) ▪ Major exclusions: Patients with chronic hyper tension or renal disease, diabetes, cardiovascular, cerebrovascular, or neurological disease, or placental or obstetric complications	Randomized, parallel, controlled ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in SBP ≥20% of baseline value or SBP <100 mmHg	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Uterine artery pulsatility index ▪ Fetal heart rate	Eph (15) All female 29.2 ± 4.7 (24 – 35)	5 mg IV bolus	Adverse events not reported Heart rate increased	All APGAR scores ≥7 at 1 min and ≥9 at 5 min All umbilical artery pH values >7.2
					Phe – bolus (15) All female 28.5 ± 2.5 (27 – 31)	25 µg IV bolus	Adverse events not reported Heart rate decreased	All APGAR scores ≥7 at 1 min and ≥9 at 5 min All umbilical artery pH values >7.2
					Phe – infusion (15) All female 27.9 ± 3.9 (23 – 32)	25 µg/min; subsequently adjusted according to SBP	Adverse events not reported Heart rate decreased	All APGAR scores ≥7 at 1 min and ≥9 at 5 min All umbilical artery pH values >7.2

(Source: NDA 208289 Applicant's table page 65 of Integrated Summary of Safety) (Mokhtar 2014)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Moran et al. 1991 (US; dates not stated) Ephedrine = Eph Phenylephrine = Phe	Singleton, pregnant, adult women undergoing elective C-section delivery	Randomized, double-blind, parallel, positive controlled ▪ Hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Any decrease in SBP to <100 mmHg or an initial decrease of ≥5 mmHg	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Early Neonatal Neurobehavioral Scale at 2 and 6 h post-delivery	Eph (29) All female Not reported	10 mg IV bolus initial then 5 – 10 mg IV bolus as needed Mean ± SD total dose = 41 ± 4 mg	Frequency of nausea and/or vomiting = 28% Mean heart rate change per minute = +13 (range -25 - +44) bpm	All APGAR scores ≥7 at 1 min except 1 neonate with a score of 6 All APGAR scores ≥9 at 5 min Umbilical artery pH mean ± SEM = 7.28 ± 0.01 Early Neonatal Behavioral Scale scores not reported but stated that there were no differences between treatment groups
					Phe (31) All female Not reported	80 µg IV bolus initial then 40 – 80 µg IV bolus as needed Mean ± SD total dose = 335 ± 31 µg	Frequency of nausea and/or vomiting = 25% Mean heart rate change per minute = -26 (range -10 - -44) bpm	All APGAR scores ≥7 at 1 min All APGAR scores ≥9 at 5 min Umbilical artery pH mean ± SEM = 7.32 ± 0.01

(Source: NDA 208289 Applicant's table page 59 of Integrated Summary of Safety) (Moran et al. 1991)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Nag 2010 (India; Dec 2007 – Dec 2008) (-)Ephedrine HC1 = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing elective or emergency C-section delivery who met hypotension threshold definition ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, or cardiac, pulmonary or renal diseases which could affect hemodynamic responses	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading	Decrease in systolic blood pressure (SBP) ≥20% or <90 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ Diastolic blood pressure (DBP) ▪ Mean arterial pressure (MAP) Neonate ▪ APGAR score	Eph (50) 26.9± 1.7 (25 – 31)	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}	Adverse events not reported Meant DBP and MAP followed similar pattern to SBP MAP is significantly lower compared to Phe Mean heart rate increased post-Eph administration	APGAR scores of 9 or 10 at 1 and 5 min post-delivery
					Phe (50) 26.8± 1.7 (23-32)	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	Adverse events not reported Mean DBP and MAP followed similar pattern to SBP MAP is significantly higher compared to Eph Mean heart rate decreased post Phe administration	APGAR scores of 9 or 10 at 1 and 5 min post-delivery

(Source: NDA 208289 Applicant's table page 9 of Integrated Summary of Safety) (Nag 2010)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2000 (China [Hong Kong]; dates not stated) (-)Ephedrine Sulfate = Eph	▪ Singleton, full-term pregnant Asian women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, cardiovascular or cerebrovascular disease	Randomized, double blind, parallel, dose-finding ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in systolic blood pressure (SAP) ≥20% or <100 mmHg	Maternal ▪ Heart rate ▪ SAP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Heart Rate	Saline Control (20) 31.2 ± 5.4	Eph10 mg {7.7 mg FB} IV bolus rescue doses (every 1 min) when hypotension definition met Mean (± SD) total dose = 29.5 (18.5) mg {22.7 (14.2) mg FB}	Nausea or vomiting = 9 pts (45%) Hypotension = 19 pts (95%) Reactive hypertension = 2 pts (10%)	All APGAR scores ≥7 at 1 and 5 min post delivery Number of cases with umbilical artery pH <7.2 = 2/19 (11%)
					Eph 10 mg (20) 32.4 ± 4.8	Please see Table 5 for data.		
					Eph 20 mg (20) 34.3 ± 3.6			
					Eph 30 mg (20) 33.0 ± 4.3			

(Source: NDA 208289 Applicant's table 2 page 21 of Integrated Summary of Safety) (Ngan Kee et al. 2000)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2000 (China [Hong Kong]; dates not stated) (-)Ephedrine Sulfate = Eph	■ Singleton, full-term pregnant Asian women undergoing elective C-section delivery ■ ASA Grade I or II Major exclusions: Patients with hypertension, cardiovascular or cerebrovascular disease	Randomized, double blind, parallel, dose-finding ■ 0.5% hyperbaric bupivacaine, fentanyl ■ Pre-anesthesia IV fluid loading ■ Positioned with left uterine displacement ■ Prophylactic ranitidine	Decrease in systolic blood pressure (SAP) ≥ 20% of baseline or <100 mmHg	Maternal ■ Heart rate ■ SAP ■ DBP Neonate ■ APGAR score ■ Umbilical arterial and venous acid-base status Heart Rate	Saline Control (20) 31.2 ± 5.4	Please see Table 2 for data.		
					Ep 10 mg (20) 32.4 ± 4.8	10 mg {7.7 mg FB} IV bolus when spinal anesthesia established 10 mg {7.7 mg FB} IV bolus rescue doses (every 1 min) when hypotension definition met Mean (± SD) total dose = 39.0 (25.3) mg {30.0 (19.5) mg FB}	Nausea or vomiting = 9 pts (45%) Hypotension = 17 pts (85%) Reactive hypertension = 1 pts (5%)	All APGAR scores ≥7 at 1 and 5 min post delivery Number of cases with umbilical artery pH <7.2 = 5/20 (25%)
					Eph 20 mg (20) 34.3 ± 3.6	20 mg {15.4 mg FB} IV bolus when spinal anesthesia established 10 mg {7.7 mg FB} IV bolus rescue doses (every 1 min) when hypotension definition met Mean (± SD) total dose = 46.5 (21.1) mg {35.8 (16.2) mg FB}	Nausea or vomiting = 13 pts (65%) Hypotension = 16 pts (80%) Reactive hypertension = 5 pts (25%)	All APGAR scores ≥7 at 1 and 5 min post delivery Number of cases with umbilical artery pH <7.2 = 8/19 (42%)
					Eph 30 mg (20) 33.0 ± 4.3	30 mg {23.1 mg FB} IV bolus when spinal anesthesia established 10 mg {7.7 mg FB} IV bolus rescue doses (every 1 min) when hypotension definition met Mean (± SD) total dose = 39.5 (16.4) mg {30.4 (12.6) mg FB}	Nausea or vomiting = 5 pts (25%) Hypotension = 7 pts (35%) Reactive hypertension = 9 pts (45%)	All APGAR scores ≥7 at 1 and 5 min post delivery Number of cases with umbilical artery pH <7.2 = 4/18 (22%)

(Source: NDA 208289 Applicant's table 5 page 48 of Integrated Summary of Safety) (Ngan Kee et al. 2000)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2001 (China [Hong Kong]; dates not stated) (-)Ephedrine Sulfate = Eph Metaraminol = Met	▪ Singleton, full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, cardiac or cerebrovascular disease, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in systolic arterial pressure (SAP) >10%	Maternal ▪ Heart rate ▪ Arterial pressure Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Uterine artery pulsatility index	Eph (25 but only 23 dosed) 32± 3	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}	5 patients had nausea or vomiting Mean heart rate increased post-Eph	One case (4%) of APGAR score <7 at 1 min All APGAR scores ≥7 at 5 min 9 (39%) fetus with umbilical arterial pH <7.2
					Met (25 but treatment data from only 23 available) 33± 4	Initial 0.5 mg IV bolus dose then 0.25 mg/min and stopped when SAP increased above baseline values Total mean ± SD dose of Met = 3.1± 0.9 mg	1 patient had nausea or vomiting Mean heart rate decreased post-Met	One case (4%) of APGAR score <7 at 1 min All APGAR scores ≥7 at 5 min No fetus with umbilical arterial pH <7.2

(Source: NDA 208289 Applicant's table page 17 of Integrated Summary of Safety) (Ngan Kee et al. 2001; Ngan Kee, Khaw, et al. 2008)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2008a (China [Hong Kong]; dates not reported) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, preexisting cardiovascular or cerebrovascular diseases, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Positioned with left uterine displacement ▪ Antacid premedication	Infusion stopped or started after initial 2 min if SBP above or below baseline value, respectively Hypotension defined as >20% decrease in SBP from baseline	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph 8 mg/mL {6.2 mg/mL FB} (25) 32 ± 4	60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Median total dose (IQR) = 54 (42 – 71) mg, {41.6 (32.3 – 54.7) mg FB}	Nausea or vomiting = 10 pts (40%) Hypotension = 8 pts (32%) Reactive hypertension = 15 (60%) Increased mean heart rate	All APGAR scores ≥7 at 1 min and ≥9 at 5 min post-delivery Median (IQR) umbilical artery pH = 7.21 (7.12 – 7.25)
					Eph 6 mg/mL {4.6 mg/mL FB} + Phe 25 µg/mL (24) 32 ± 4	60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Eph median total dose (IQR) = 41 (32 – 49) mg, {31.6 (24.6 – 37.7) mg FB} Phe median total dose (IQR) = 169 (131 - 204) µg	Nausea or vomiting = 5 pts (21%) Hypotension = 2 pts (8%) Reactive hypertension = 8 (33%)	All APGAR scores ≥7 at 1 min and ≥9 at 5 min post-delivery Median (IQR) umbilical artery pH = 7.24 (7.20 – 7.28)
					Eph 4 mg/mL {3.1 mg/mL FB} + Phe 50 µg/mL (25) 30 ± 5	60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Eph median total dose (IQR) = 33 (29 – 37) mg, {25.4 (22.3 – 28.5) mg FB} Phe median total dose (IQR) = 410 (360 - 460) µg	Nausea or vomiting = 0 pts Hypotension = 3 pts (12%) Reactive hypertension = 9 (36%)	All APGAR scores ≥7 at 1 min and ≥9 at 5 min post-delivery Median (IQR) umbilical artery pH = 7.26 (7.21 – 7.29)

(Source: NDA 208289 Applicant's table page 40 of Integrated Summary of Safety) (Ngan Kee, Lee, et al. 2008)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2008a (Continued) (China [Hong Kong]; dates not reported) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe					Eph 2 mg/mL {1.5 mg/mL FB} + Phe 75 µg/mL (24) 31 ± 3	60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Eph median total dose (IQR) = 18 (15 – 20) mg, {13.9 (11.6 – 15.4) mg FB} Phe median total dose (IQR) = 679 (660 - 765) µg	Nausea or vomiting = 4 pts (17%) Hypotension = 3 pts (13%) Reactive hypertension = 13 (54%)	All APGAR scores ≥7 at 1 min and ≥9 at 5 min post-delivery Median (IQR) umbilical artery pH = 7.28 (7.23 – 7.30)
					Phe 100 µg/mL (24) 32 ± 4	60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Median total dose (IQR) = 890 (650 – 1085) µg	Nausea or vomiting = 0 pts Hypotension = 1 pt (4%) Reactive hypertension = 12 (50%) Decreased mean heart rate	All APGAR scores ≥7 at 1 min and ≥9 at 5 min post-delivery Median (IQR) umbilical artery pH = 7.29 (7.28 – 7.30)

(Source: NDA 208289 Applicant's table page 41 of Integrated Summary of Safety) (Ngan Kee, Lee, et al. 2008)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2008b (China [Hong Kong]; dates not stated but enrollment occurred over 2 years) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	Note: demographics and safety reported for entire treatment group population (n = 102/group) not the 73% who met hypotension threshold definition ▪ Singleton pregnant women undergoing non-elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, cardiovascular or cerebrovascular disease, fetal abnormality	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, 15 µg fentanyl ▪ IV fluid loading just after anesthesia	SBP <100 mmHg	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (74) 30 ± 4.3	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	Nausea or vomiting = 13/102 (13%)	APGAR scores all ≥7 at 1 and 5 min except for one neonate 21 (21%) neonates admitted to special care baby unit One neonate admitted to neonatal intensive care unit due to feto-maternal transfusion syndrome UA and VA PO_2 were significantly higher than Phe group
					Phe (74) 31 ± 4.9	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	Nausea or vomiting = 4/102 (4%)	All APGAR scores ≥7 at 1 min except for one neonate All APGAR scores ≥7 at 5 min 17 (17%) neonates admitted to special care baby unit UA and VA PO_2 were significantly lower than Eph group

(Source: NDA 208289 Applicant's table page 11 of Integrated Summary of Safety) (Ngan Kee, Khaw, et al. 2008)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ngan Kee et al. 2009 (China [Hong Kong]; dates not reported) (-)Ephedrine Sulfate = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, preexisting cardiovascular or cerebrovascular diseases, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine, fentanyl ▪ Positioned with left uterine displacement	Infusion stopped or started after initial 2 min if SBP above or below baseline value, respectively Hypotension defined as >20% decrease in SBP from baseline If >2 episodes of hypotension, IV bolus of 100 µg phenylephrine given	Maternal ▪ Heart rate ▪ SBP ▪ Arterial blood sampling for active drug, epinephrine, norepinephrine, lactate and glucose Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status and active drug, epinephrine, norepinephrine, lactate and glucose	Eph (52) 32 ± 4.7	8 mg/mL {6.2 mg/mL FB} at 60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Estimated median total dose (IQR) = 61.6 (45 – 79) mg, {47.4 (34.7 – 60.8) mg FB}	Nausea or vomiting = 18 pts (35%) Hypotension = 13 pts (25%) with 11 pts (22%) receiving rescue Phe Reactive hypertension = 24 pts (47%) Median (IQR) Eph arterial conc = 367 (307 – 524) ng/mL, {282.6 (236.4 – 403.5) ng/mL FB}	All APGAR scores ≥7 at 1 min and 5 min post-delivery Median (IQR) umbilical artery pH = 7.25 (7.14 – 7.29) Median (IQR) Eph umbilical arterial conc = 355 (255 – 545) ng/mL, {273.4 (196.4 – 419.7) ng/mL FB} Median (IQR) Eph umbilical venous conc = 435 (334 – 594) ng/mL, {335.0 (257.2 – 457.4) ng/mL FB}
					Phe (52) 32 ± 4.7	100 µg/mL at 60 mL/h for initial 2 min following administration of anesthesia then per blood pressure algorithm Estimated median total dose (IQR) = 1300 (960 – 1690) µg	Nausea or vomiting = 1 pt (2%) Hypotension = 2 pts (4%) with 1 pt (2%) receiving rescue Phe Reactive hypertension = 21 pts (41%)	All APGAR scores ≥7 at 1 min and 5 min post-delivery except for 1 case of a score of 6 at 1 min Median (IQR) umbilical artery pH = 7.33 (7.30 – 7.35)

(Source: NDA 208289 Applicant's table page 42 of Integrated Summary of Safety) (Ngan Kee et al. 2009)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Nissen et al. 2010 (Denmark; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	■ Adult female patients undergoing elective mastectomy, thyroidectomy, or parathyroidectomy who met hypotension threshold definition ■ ASA Grade I or II ■ Major exclusions: Patients with treatment for hypertension, previous treatment with bleomycin, or raised values of bilirubin	Open label, sequential series ■ Induction = 0.15 mg fentanyl, 2 mg/kg propofol ■ Maintenance = 25 - 33 µg/kg/min propofol,	Decrease in MAP to <60 mmHg	• Heart rate • MAP • Cardiac output • Frontal lobe oxygenation • Total peripheral resistance	Eph (12) All females 53 ± 19	10 mg {8.2 mg FB} IV bolus	Not reported	Restored anesthesia-related decrease in cardiac output Slight increase in mean heart rate but no change in cerebral oxygenation or total peripheral resistance
					Phe (13) All females 59 ± 10	100 µg IV bolus	Not reported	No effect on cardiac output Decreased heart rate and decreased (14%) cerebral oxygenation Increased total peripheral resistance

(Source: NDA 208289 Applicant's table page 32 of Integrated Summary of Safety) (Nissen et al. 2010)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Odagme et al. 2013 (Nigeria; dates not reported) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with preeclampsia, coagulation or bleeding disorders, neurological disorders, severe heart disease, or intercurrent medical diseases	Randomized, double-blind, parallel, positive control ▪ 0.5% isobaric bupivacaine, 2% lidocaine epidural as needed ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SBP ≥20% of baseline value Treated with IV bolus of 50% of initial treatment dose	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (29) 32.6 ± 4.7	1 mg/min {0.82 mg/mL FB} Mean (± SD) total dose = 5.0 (1.1) mg, {4.1 (0.90) mg FB}	Nausea = 0 pt Vomiting = 0 pt Shivering = 5 pts (17%) Tachycardia = 0 pt Hypotension = 3 pts (10%) Reactive hypertension = 1 pt (3%) 3 pts (10%) required epidural use	Only mean APGAR and umbilical artery pH values reported – did not differ between treatments
					Phe (30) 32.6 ± 4.7	80 µg/min Mean (± SD) total dose = 426 (123.6) µg	Nausea = 1 pt (3%) Vomiting = 1 pt (3%) Shivering = 3 pts (10%) Tachycardia = 3 pts (10%) Hypotension = 2 pts (7%) Reactive hypertension = 3 pts (10%) 2 pts (7%) required epidural use	

(Source: NDA 208289 Applicant's table page 47 of Integrated Summary of Safety) (Odagme MT 2013)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Pennekamp et al. 2011 (Netherlands; Feb 2009 – Jun 2011) (-)Ephedrine HCl = Eph Phenylephrine = Phe	Patients undergoing carotid endarterectomy	Comparative, parallel, positive control ▪ Not reported but same anesthetic regimen used for all patients	Decrease in mean arterial pressure (MAP) >20%	• Heart rate • MAP • Cardiac output • Frontal lobe oxygenation • Mean middle cerebral artery blood velocity	Eph (7) Not reported	5 – 10 mg {4.1 – 8.2 mg FB} IV bolus	Not reported	Heart rate increased Frontal lobe oxygenation increased Cerebral artery blood velocity remained constant
					Phe (4) Not reported	50 – 100 µg IV bolus	Not reported	Heart rate decreased Frontal lobe oxygenation decreased Cerebral artery blood velocity increased

(Source: NDA 208289 Applicant's table page 34 of Integrated Summary of Safety) (Pennekamp et al. 2012)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Prakash et al. 2010 (India; dates not stated) (-)Ephedrine HCl = Eph Phenylephrine = Phe	▪ Singleton pregnant women undergoing elective C-section delivery who met hypotension threshold definition ▪ ASA Grade I ▪ Major exclusions: Patients with hypertension, diabetes, cardiac or cerebrovascular disease, or fetal abnormalities	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine and metoclopra-mide	Decrease in systolic blood pressure (SBP) ≥20%	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Neuro-behavioral scores	Eph (30) 24.5± 4.4	6 mg {4.9 mg FB} IV bolus whenever SBP dropped below pre-specified threshold Mean Number of Doses = 2 (range 1 – 4) Mean ± SD Total Dose = 12.5 ± 5.1 mg {10.3 ± 4.2 mg FB}	Nausea (n = 4 [13%]) patients Vomiting (n = 1 [3%]) patient No patient had a heart rate < 60 bpm 13 (43%) patients had a heart rate of > 100 bpm	APGAR scores of 7 – 10 at 1, 5, and 10 min post-delivery No umbilical artery pH values <7.2 Low neuro- behavioral scores generally recovered by 48 h post-delivery
					Phe (30) 24.1± 4.4	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	Nausea or vomiting n = 0 5 (17%) of patients had a heart rate <60 bpm with 3 (10%) patients requiring IV atropine 6 (20%) patients had a heart rate of >100 bpm	APGAR scores of 8 – 10 at 1, 5, and 10 min post-delivery No umbilical artery pH values <7.2 Low neuro- behavioral scores generally recovered by 48 h post-delivery

(Source: NDA 208289 Applicant's table page 10 of Integrated Summary of Safety) (Prakash et al. 2010)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Puri and Talwar 2010 (India; dates not stated) Ephedrine = Eph Mephentermine = Mep	■ Patients >60 years undergoing urologic surgical procedure and meeting hypotension threshold after spinal anesthesia ■ ASA Grade I or II ■ Major exclusions: Patients with diabetes, severe cardiovascular or respiratory disease	Randomized, double-blind, parallel, positive control ■ 0.5% hyperbaric bupivacaine ■ Premedication with diazepam	Decrease in SAP >25% of baseline or <90 mmHg	■ Heart rate ■ Systolic, diastolic, and mean arterial pressure ■ Central venous pressure	Eph (20) 14M/6F 66.6 ± 3.2	10 mg IV bolus then 30 mg/h (0.6 mg/kg/hr) infusion	Not reported	Heart rate increased Slight increase in central venous pressure after Eph
					Mep (20) 15M/5F 66.0 ± 2.3	10 mg IV bolus then 60 mg/h (1 mg/min) infusion	Not reported	Heart rate increased Slight increase in central venous pressure after Mep

(Source: NDA 208289 Applicant's table page 71 of Integrated Summary of Safety) (Puri 2010)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Ramanathan and Grant 1988 (US; dates not specified) Ephedrine = Eph Phenylephrine = Phe	Uncomplicated, singleton full-term pregnant women undergoing repeat elective C-section delivery	Randomized, open label, parallel, positive control ▪ Epidural: 1.5% lidocaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displace-ment	Decrease in SBP <100 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP ▪ Pre-ejection period ▪ Ventricular ejection time Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Fetal heart rate	Eph (40) All female Not reported	5 mg IV bolus 1 bolus only = 19 pts 2 bolus = 11 pts 3 bolus = 10 pts	Not reported	2 neonates with APGAR scores <7 at 1 min 1 neonate with APGAR score <9 at 5 min No difference from control group in umbilical arterial and venous acid-base status
					Phe (40) All female Not reported	100 µg IV bolus 1 bolus only = 17 pts 2 bolus = 15 pts 3 bolus = 8 pts	Not reported	2 neonates with APGAR scores <7 at 1 min 1 neonate with APGAR score <9 at 5 min No difference from control group in umbilical arterial and venous acid-base status
					Untreated – SBP >100 mmHg (57) All female Not reported	Not applicable	Not reported	3 neonates with APGAR scores <7 at 1 min 1 neonate with APGAR score <9 at 5 min

(Source: NDA 208289 Applicant's table page 74 of Integrated Summary of Safety) (Ramanathan and Grant 1988)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Rehman et al. 2011 (Pakistan; Oct 2007 – Mar 2008) Ephedrine = Eph	▪ Pregnant, adult women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension or receiving anti-hypertensives, diabetes, preeclampsia or eclampsia, or obstetric complications	Randomized, double-blind, parallel ▪ 0.75% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SBP >30% of baseline value	Maternal ↓ Heart rate ↓ SBP	Eph – SBP threshold drop (35 but only 23 met hypotension threshold) All female 31 ± 4	10 mg IV bolus 23 (66%) pts met hypotension threshold criteria and required dose 8 of these pts received a second bolus dose Mean ± SD total dose = 12.2 ± 4 mg	Nausea = 5 (14%) pts	Not reported
					Eph – with-anesthesia as prohylatic (35) All female 27 ± 4	15 mg IV with anesthesia agent then 10 mg IV bolus if needed 6 (17%) pts required rescue 10 mg dose Mean ± SD total dose = 16.7 ± 4 mg	Nausea = 2 (6%) pts	Not reported

(Source: NDA 208289 Applicant's table page 61 of Integrated Summary of Safety) (Rehman 2011; Simin 2012)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Simin et al. 2012 (Iran; dates not stated but enrollment over 6 months) Ephedrine = Eph Phenylephrine = Phe	▪ Full-term pregnant, adult women undergoing elective C-section delivery ▪ ASA Grade I ▪ Major exclusions: Patients with pre-existing systemic disease, history of taking medications that could influence hemodynamic responses	Double blind, parallel, positive control ▪ 5% hyperbaric lidocaine, 15 µg fentanyl ▪ Pre-anesthesia IV fluid loading	Decrease in SAP ≥20% of baseline value	Maternal ▪ Heart rate ▪ SAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (33) All female 28.1 ± 4.9	5 mg IV bolus Median number of boluses = 2 (range 1 – 3) Mean ± SD total dose = 8.4 ± 0.9 mg	Nausea and/or vomiting = 5 (15%) pts	All APGAR scores ≥8 at 1 min and 5 min All umbilical artery pH values >7.2
					Phe (27) All female 29.6 ± 4.9	100 µg IV bolus Median number of boluses = 2 (range 1 –2) Mean ± SD total dose = 123.3 ± 40.0 µg	Nausea and/or vomiting = 2 (7%) pts	All APGAR scores ≥8 at 1 min and 5 min All umbilical artery pH values >7.2

(Source: NDA 208289 Applicant's table page 63 of Integrated Summary of Safety) (Simin 2012)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)**	**Dose/Regimen**	**Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Safety-Related Findings**	
								Adverse Events	**Other Safety Related Outcomes**
Taguchi et al. 1996 (Japan; dates not stated) Ephedrine Hydrochloride = Eph	▪ Pediatric patients (ages 0.1 to 15 years) surgery under general anesthesia ▪ ASA Grade I	Parallel, Dose-Finding ▪ General anesthesia induction with halothane 2% inspired and 67% nitrous oxide ▪ Maintenance: 1.0 MAC halothane and 67% nitrous oxide ▪ Pre-anesthesia IV fluid loading	When a steady state of end-tidal halothane concentration and hemodynamic period of at least 5 min was established, Eph was injected IV as a bolus. Though baseline MAP was not recorded, based on the knowledge that some degree of hypotension typically follows induction of anesthesia, these patients are considered to be at least slightly hypotensive at the time of treatment with Eph	▪ Heart rate ▪ MAP ▪ pHa ▪ $PaCO_2$ ▪ PaO_2	A-1: age < 1.0 years (9)	0.1 mg/kg {0.08 mg/kg FB} Eph IV bolus	5F/12M Age 0.4 ± 0.3 (0.1 – 0.9)	The differences in arterial blood gas tensions among groups were not significant. When maximum percent change in HR was analyzed, there were no significant differences between the groups. For most patients, an increased heart rate post-ephedrine was observed.	
					A-2: age < 1.0 years (8)	0.2 mg/kg {0.16 mg/kg FB} Eph IV bolus			
					B-1: age 1 – 1.99 years (8)	0.1 mg/kg {0.08 mg/kg FB} Eph IV bolus	4F/15M Age 1.3 ± 0.3 (1.0 – 1.9)		
					B-2: age 1 – 1.99 years (11)	0.2 mg/kg {0.16 mg/kg FB} Eph IV bolus			
					C-1: age 2 – 5.99 years (21)	0.1 mg/kg {0.08 mg/kg FB} Eph IV bolus	15F/26M Age 3.8 ± 1.1 (2.0 – 5.9)		
					C-2: age 2 – 5.99 years (20)	0.2 mg/kg {0.16 mg/kg FB} Eph IV bolus			
					D-1: age 6 – 9.99 years (10)	0.1 mg/kg {0.08 mg/kg FB} Eph IV bolus	9F/12M Age 7.4 ± 1.3 (6.0 – 9.8)		
					D-2: age 6 – 9.99 years (11)	0.2 mg/kg {0.16 mg/kg FB} Eph IV bolus			
					E-1: age ≥ 10 years (7)	0.1 mg/kg {0.08 mg/kg FB} Eph IV bolus	7F/5M Age 12.8 ± 1.6 (10.0 – 14.3)		
					E-2: age ≥ 10 years (5)	0.2 mg/kg {0.16 mg/kg FB} Eph IV bolus			

(Source: NDA 208289 Applicant's table page 78 of Integrated Summary of Safety) (Taguchi et al. 1996)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Taivainen 1991 (Finland; dates not stated) Ephedrine HCl = Eph Etilefrine = Eti	▪ Elderly patients undergoing hip surgery and meeting hypotension threshold after spinal anesthesia ▪ ASA Grade II or III ▪ Major exclusions: age <65, medication for hypertension, or decompensation of the heart.	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Premedication with diazepam and fentanyl; fentanyl only for hip fracture patients	Decrease in MAP >25% of baseline	▪ Heart rate ▪ Systolic, diastolic, and mean arterial pressure ▪ Central venous pressure	Eph (15) 6M/9F 74.0 ± 6.8	0.07 mg/kg {0.57 mg/kg FB} IV bolus Mean ± SD of number of boluses = 3.8 ± 1.9 (≥6 boluses needed in 3 pts) Mean ± SD total dose = 4.9 ± 1.0 mg {4.0 ± 0.8 mg FB}	Nausea = 1 pt 30 min after initial dose of Eph	Maximum mean change from baseline in heart rate = 6.0% Slight increase in central venous pressure
					Eti (15) 6M/9F 75.2 ± 5.7	0.03 mg/kg IV bolus Mean ± SD of number of boluses = 3.6 ± 2.2 (≥6 boluses needed in 3 pts Mean ± SD total dose = 2.0 ± 0.4	Angina pectoris with ST-segment depression = 1 pt (after dose 5) with coronary artery disease	Maximum mean change from baseline in heart rate = 6.1% Slight increase in central venous pressure

(Source: NDA 208289 Applicant's table page 70 of Integrated Summary of Safety) (Taivainen 1991)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Adverse Events	**Other Safety Related Outcomes**
Tanaka and Dohi 1994 (Japan; dates not stated) Ephedrine = Eph Phenylephrine = Phe	■ Adult patients undergoing surgery for lung lobectomy or pneumonectomy, liver lobectomy, or total cystectomy ■ ASA Grade II ■ Major exclusions: Patients with cardiovascular complications and/or chronic obstructive lung diseases	Open label, positive control Patients were stratified based on whether they had a cervical epidural, lumbar epidural, or enflurane with nitrox oxide supplementation ■ Epidural: 1.5% lidocaine with epinephrine ■ General anesthesia induction: thiamylal 4 - 5 mg/kg and 6 mg pancuronium or 1 mg/kg succinylcholine ■ Maintenance: Nitrous oxide ■ Premedication with diazepam	Decrease in arterial pressure >20% of baseline	■ Heart rate ■ Arterial blood pressure ■ Pulmonary arterial pressure ■ Right atrial pressure ■ Cardiac output ■ $P_{ET}CO_2$	Eph (26) 20M/6F Age ranges: 53 ± 14 to 68 ± 8	0.2 ± 0.05 mg/kg IV bolus	No arrhythmia was observed in any patient in either treatment group	Post-Eph increases in blood pressure and pulmonary arterial pressure were similar across subgroups. Post-Eph increase in cardiac output
					Phe (26) 24M/2F Age ranges: 53 ± 11 to 65 ± 10	2.5 ± 0.8 µg/kg IV bolus		Decrease in heart rate in all subgroups Post-Phe increases in blood pressure and pulmonary arterial pressure were similar across subgroups.

(Source: NDA 208289 Applicant's table page 77 of Integrated Summary of Safety) (Tanaka and Dohi 1994)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Thomas et al. 1996 (United Kingdom; dates not stated) Ephedrine = Eph Phenylephrine = Phe	Singleton, pregnant, adult women undergoing elective C-section delivery	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic ranitidine	Decrease in systolic arterial pressure (SAP) >10% of baseline value	Maternal ▪ Heart rate ▪ SAP ▪ CO Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Umbilical artery pulsatility index ▪ Fetal heart rate	Eph (20) All female 27.4	5 mg IV bolus Median (range) of number of bolus doses = 4 (1 - 8)	Adverse events not reported Maximum mean (95% CI) change in heart rate values from baseline: -14.4 (-18.2, -10.6) % Maximum mean (95% CI) percent change in CO = -5.6 (-10.2, -0.9)	All APGAR scores ≥7 at 1 and 5 min Umbilical artery pH mean (95% CI) = 7.27 (7.25, 7.28) with 1 neonate with a pH <7.2 Mean (95% CI) percent change in umbilical pulsatility index = -0.8 (-2.4, 4.0) Mean (95% CI) percent change from baseline in fetal heart rate = 0.8 (-2.3, 3.8)
					Phe (20) All female 30.0	100 µg IV bolus Median (range) of number of bolus doses = 6 (1 - 10)	Adverse events not reported Maximum mean (95% CI) change in heart rate values from baseline: 28.5 (-32.9, -24.2) % Maximum mean (95% CI) percent change in CO = -8.9 (-14.6, -3.1)	All APGAR scores ≥7 at 1 and 5 min Umbilical artery pH mean (95% CI) = 7.29 (7.28, 7.30) with no neonate with a pH <7 Mean (95% CI) percent change in umbilical pulsatility index = 0.7 (-3.3, 4.8)) Mean (95% CI) percent change from baseline in fetal heart rate = -4.3 (-7.4, -1.2)

(Source: NDA 208289 Applicant's table page 58 of Integrated Summary of Safety) (Thomas et al. 1996)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Turkoz et al. 2002 (Turkey; dates not stated) Ephedrine HCl = Eph	▪ Singleton full-term pregnant women undergoing elective C-section delivery ▪ Major exclusions: Patients with hypertension, diabetes, or obstetric complications	Randomized, double-blind, parallel ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SAP >20% of baseline value	Maternal ▪ Heart rate ▪ SAP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph – bolus (15 but only 13 pts dosed) All female 27.9 ±4.6	10 mg IV bolus 1/13 pts required > 1 bolus (4 bolus doses) Mean ± SD total dose = 29.7 ± 8.5 mg {24.4 ± 7.0 mg FB}	Nausea = 10 (66%) pts Increased heart rate post-Eph	All APGAR scores ≥7 at 1 min and ≥9 at 5 min except 1 neonate with APGAR score of 1 at 1 min (no further details reported) Umbilical artery pH mean ± SD = 7.28 ± 0.04
					Eph – post-anesthesia prohylatic (15) All female 26.8 ±3.8	IV infusion of 5 mg/min immediately following administration of anesthetic agent – complex dosing algorithm described Mean ± SD total dose = 33.5 ± 7.7 mg	Nausea = 1 (6%) pt Increased heart rate post-Eph	All APGAR scores ≥7 at 1 min and ≥9 at 5 min Umbilical artery pH mean ± SD = 7.34 ± 0.02

(Source: NDA 208289 Applicant's table page 62 of Integrated Summary of Safety) (Turkoz et al. 2002)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Vercauteren et al. 2000 (Belgium; dates not reported) (-)Ephedrine HCl = Eph	▪ Full-term pregnant women undergoing elective C-section delivery ▪ Major exclusions: Patients with initial SBP >150 mmHg	Double-blind, controlled, parallel ▪ Bupivacaine, sufentanil: Epidural supplement of 2% lidocaine allowed if needed ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic cimetidine with Na citrate	Decrease in SBP >30% of baseline or <100 mmHg, if heart rate decreased by more than 30% of baseline, or when patients complained of nausea or feeling faint	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Saline (24) 30 ± 5	If hypotension, heart rate or symptomatic criteria met received IV bolus 5 mg {4.1 mg FB} Eph Mean (± SD) number of supplemental Eph doses = 1.7 (1.7)	Nausea = 16 pt (67%) Vomiting = 1 pt (4%)	APGAR scores and umbilical pH not different between groups
					Eph (24) 29 ± 4	Please see Table 5 for data.		

(Source: NDA 208289 Applicant's table 2 page 23 of Integrated Summary of Safety) (Vercauteren et al. 2000)

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Vercauteren et al. 2000 (Belgium; dates not reported) (-)Ephedrine HCl = Eph	▪ Full-term pregnant women undergoing elective C-section delivery ▪ Major exclusions: Patients with initial SBP >150 mmHg	Randomized, double-blind, controlled, parallel ▪ Bupivacaine, sufentanil: Epidural supplement of 2% lidocaine allowed if needed ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic cimetidine with Na citrate	Decrease in SBP >30% of baseline or <100 mmHg, if heart rate decreased by more than 30% of baseline, or when patients complained of nausea or feeling faint	Maternal ▪ Heart rate ▪ SBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Saline (24) 30 ± 5	Please see Table 2 for data.		
					Eph (24) 29 ± 4	5 mg {4.1 mg FB} IV bolus immediately after spinal anesthesia administered If hypotension, heart rate or symptomatic criteria met received IV bolus 5 mg {4.1 mg FB} Eph Mean (± SD) number of supplemental Eph doses = 0.5 (0.8)	Nausea = 9 pt (38%) Vomiting = 1 pt (4%)	APGAR scores and umbilical pH not different between groups

(Source: NDA 208289 Applicant's table 5 page 52 of Integrated Summary of Safety) (Vercauteren et al. 2000)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Videira et al. 2000 (abstract only) (-)Ephedrine Sulfate = Eph	Full-term pregnant women undergoing C-section delivery	Not reported ▪ Bupivacaine ▪ Positioned with left uterine displacement	SAP <100 mmHg Any patient meeting this criteria received IV bolus Eph 10 mg {7.7 mg FB}	Maternal SAP	Eph IV bolus (30) Not reported	10 mg {7.7 mg FB} IV bolus following spinal anesthesia administration and 5 mg {3.9 mg FB} IV bolus whenever SAP 10 mmHg lower than baseline value Total dose not reported	Hypotension in 17% of pts	None reported
					Eph IV infusion (30) Not reported	0.1 mg/mL {0.077 mg/mL FB} Eph infusion starting after spinal anesthesia administration to maintain SAP within 10 mmHg of baseline value Total dose not reported	Hypotension in 30% of pts	
					Eph IV bolus and infusion (30) Not reported	10 mg {7.7 mg FB} IV bolus then 0.1 mg/mL {0.077 mg/mL FB} infusion after spinal anesthesia administration to maintain SAP within 10 mmHg of baseline value Total dose not reported	Hypotension in 13% of pts	
					No prophyl-actic treatment with Eph (30) Not reported	10 mg {7.7 mg FB} IV bolus when SAP <100 mmHg Total dose not reported	Hypotension in 47% of pts	

(Source: NDA 208289 Applicant's table page 46 of Integrated Summary of Safety) (Videira 2000)

Literature Citation (Study Site Location; Dates of Study Conduct)	Patient Population	Study Design Anesthesia Used and Related Surgical Procedures	Hypotension Threshold Used for Initiation of Treatment	Safety Endpoints Reported	Treatment Groups (n) Gender (M/F) Age (mean ± SD; min, max in years)	Dose/Regimen	Safety-Related Findings	
							Maternal	Neonate
Wright et al. 1992 (United Kingdom [Northern Ireland]; dates not stated) Ephedrine = Eph Methoxamine = Methox	▪ Uncomplicated, singleton full-term pregnant women undergoing elective C-section delivery	Randomized, double blind, parallel, positive control ▪ Epidural: 2% lidocaine with epinephrine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement	Decrease in SBP >15% from baseline or <90 mmHg	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Uterine and umbilical artery pulsatility index ▪ Fetal heart rate	Eph (17) All female 31 ± 5	12 mg IV bolus then after 5 min 12 mg infusion over subsequent 10 min Additional 3 mg IV bolus allowed Mean (95% CI) total dose = 25.1 (23.4, 26.7) mg	Nausea common in both treatment groups (70% of patients) but resolved after vasopressor administration Mean (95% CI) maximum change in heart rate = -2.5 (-23, 18) bpm post-Eph	All APGAR scores were ≥7 at 1 min and ≥8 at 5 min post-delivery Fetal heart rate, uteroplacental and umbilical pulsatility index decreased slightly
					Methox (15) All female 29 ± 5	2 mg IV bolus then 2 mg as an infusion Additional 0.5 mg IV bolus allowed Mean (95% CI) total dose = 4.5 (4.0, 5.0) mg	Nausea common in both treatment groups (70% of patients) but resolved after vasopressor administration Mean (95% CI) maximum change in heart rate = -24 (-32, -16) bpm post-Methox	All APGAR scores were ≥7 at 1 min and ≥9 at 5 min post-delivery Fetal heart rate decreased significantly; uteroplacental and umbilical pulsatility index increased slightly
					Untreated – SBP did not reach threshold decrease (15) All female 27 ± 4	Not applicable	Slight increase in heart rate	All APGAR scores were ≥7 at 1 min and ≥9 at 5 min post-delivery Fetal heart rate, uteroplacental and umbilical pulsatility index did not change significantly

(Source: NDA 208289 Applicant's table page 75 of Integrated Summary of Safety) (Wright et al. 1992)

Literature Citation (Study Site Location; Dates of Study Conduct)	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Gender (M/F)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Xu and Wang 2013 (Republic of China; Mar 2010 – June 2012) Ephedrine = Eph Phenylephrine = Phe	▪ Singleton full-term pregnant women undergoing C-section delivery	Randomized, double-blind, parallel, positive control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading	Decrease in SBP ≥20% of baseline value	Maternal ▪ Heart rate ▪ SBP ▪ Blood concentrations of treatment drugs and epinephrine and norepinephrine at delivery Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status ▪ Blood concentrations of treatment drugs and epinephrine and nor-epinephrine at delivery	Eph (60) All female 25.5 ± 4.2	8 mg IV bolus Mean ± SD number of bolus doses = 4 ± 1	Nausea and/or vomiting = 16 pts Bradycardia = 1 pt Mean ± SD Eph arterial blood concentration (ng/mL) = 351.1 ± 63.4	APGAR scores not different between treatments Umbilical artery pH mean ± SD = 7.26 ± 0.03 Mean ± SD Eph umbilical venous blood concentration (ng/mL) = 421.0 ± 102.3 Mean ± SD Eph umbilical arterial blood concentration (ng/mL) = 360.2 ± 103.7
					Phe (60) All female 24.9 ± 4.6	100 µg IV bolus Mean ± SD number of bolus doses = 3 ± 1	Nausea and/or vomiting = 2 pts Bradycardia = 8 pts	APGAR scores not different between treatments Umbilical artery pH mean ± SD = 7.34 ± 0.03

(Source: NDA 208289 Applicant's table page 64 of Integrated Summary of Safety) (Xu 2013)

Reference ID: 3923762

Literature Citation (Study Site Location; Dates of Study Conduct) Study Drug	**Patient Population**	**Study Design** **Anesthesia Used and Related Surgical Procedures**	**Hypotension Threshold Used for Initiation of Treatment**	**Safety Endpoints Reported**	**Treatment Groups (n)** **Age (mean ± SD; min, max in years)**	**Dose/Regimen**	**Safety-Related Findings**	
							Maternal	**Neonate**
Yousefshahi et al. 2010 (Iran; dates not stated) (-)Ephedrine HCl = Eph	▪ Singleton, full-term pregnant women undergoing elective C-section delivery ▪ ASA Grade I or II ▪ Major exclusions: Patients with hypertension, diabetes, cardiovascular cerebrovascular, autoimmune, renal, or liver disease, or psychological instability or agitation	Open label, parallel, untreated control ▪ 0.5% hyperbaric bupivacaine ▪ Pre-anesthesia IV fluid loading ▪ Positioned with left uterine displacement ▪ Prophylactic H_2 antagonist	Decrease in SBP >20% for Eph treatment group but untreated group were same patient population who did not meet the hypotension threshold	Maternal ▪ Heart rate ▪ SBP ▪ DBP Neonate ▪ APGAR score ▪ Umbilical arterial and venous acid-base status	Eph (40) 29.5± 4.5 (19 – 40 years)	5- 10 mg {4.1 – 8.2 mg FB} IV bolus (number of boluses or total dose not reported)	Nausea and vomiting reported but frequency not clear	All APGAR scores were ≥8 at 1 min and ≥9 at 5 min Mean umbilical arterial pH >7.2
					No treatment (40) 29.4± 5.9 (19 – 44 years)	Not applicable	Nausea and vomiting reported but frequency not clear	All APGAR scores were ≥8 at 1 min and ≥9 at 5 min Mean umbilical arterial pH >7.2

(Source: NDA 208289 Applicant's table page 18 of Integrated Summary of Safety) (Yousefshahi 2010)

9.6 References

Abdalla, Esam E.M.; Wahba, Ola M.; Mohammed, Mahmoud A.; Almaz, Mohammed G. 2014. 'Ephedrine versus phenylephrine effects on fetal outcome and hemodynamics of pre-eclmaptic mothers undergoing cesarean section under spinal anesthesi', *Ain-Shams Journal of Anesthesiology*, 7: 215-20.

Adigun, T. A., S. D. Amanor-Boadu, and O. A. Soyannwo. 2010. 'Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia', *Afr J Med Med Sci*, 39: 13-20.

American_Sales_Company. July 2009. "CARE ONE SUPHEDRINE NASAL DECONGESTANT NON DROWSY Product Packaging." In.

Balcan, A.; Cindea, I.; Gherghina, V.; Nicolae, G. 2011. 'Spinal anaesthesia for caesarean section: Comparison of maternal and neonatal effects of bolus administration of ephedrine and phenylephrine', *European Journal of Anaesthesiology*, 28: 160.

Belzarena, S. D. 2006. '[Ephedrine and etilefrine as vasopressor to correct maternal arterial hypotension during elective cesarean section under spinal anesthesia. Comparative study]', *Rev Bras Anestesiol*, 56: 223-9.

Berends, N., A. Teunkens, E. Vandermeersch, and M. Van de Velde. 2005. 'A randomized trial comparing low-dose combined spinal-epidural anesthesia and conventional epidural anesthesia for cesarean section in severe preeclampsia', *Acta Anaesthesiol Belg*, 56: 155-62.

Bhattarai, B., S. Y. Bhat, and M. Upadya. 2010. 'Comparison of bolus phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anesthesia in cesarean section', *JNMA J Nepal Med Assoc*, 49: 23-8.

Clark, V. A., G. H. Sharwood-Smith, and A. V. Stewart. 2005. 'Ephedrine requirements are reduced during spinal anaesthesia for caesarean section in preeclampsia', *Int J Obstet Anesth*, 14: 9-13.

Cooper, D. W., M. Carpenter, P. Mowbray, W. R. Desira, D. M. Ryall, and M. S. Kokri. 2002. 'Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery', *Anesthesiology*, 97: 1582-90.

Cooper, D. W., S. C. Gibb, T. Meek, S. Owen, M. S. Kokri, A. T. Malik, and K. K. Koneti. 2007. 'Effect of intravenous vasopressor on spread of spinal anaesthesia and fetal acid-base equilibrium', *Br J Anaesth*, 98: 649-56.

Critchley, L. A., J. C. Stuart, F. Conway, and T. G. Short. 1995. 'Hypotension during subarachnoid anaesthesia: haemodynamic effects of ephedrine', *Br J Anaesth*, 74: 373-8.

Damevski, V., G. Damevska, M. Krivasija, O. Nojkov, and A. Sivevski. 2011. 'Caesarean section in isobaric spinal anesthesia with and without direct preoperative hydration with crystalloids', *Bratisl Lek Listy*, 112: 459-62.

Datta, S., M. H. Alper, G. W. Ostheimer, and J. B. Weiss. 1982. 'Method of ephedrine administration and nausea and hypotension during spinal anesthesia for cesarean section', *Anesthesiology*, 56: 68-70.

Defossez, T.; Lauwers, M.; Camu, F. 2007. 'A comparison of ephedrine and phenylephrine boluses versus continuous infusion of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery.', *Acta Anæsthesiologica Belgica*, 58: 66.

Desalu, I., and O. T. Kushimo. 2005. 'Is ephedrine infusion more effective at preventing hypotension than traditional prehydration during spinal anaesthesia for caesarean section in African parturients?', *Int J Obstet Anesth*, 14: 294-9.

Dhungana, Y., B. K. Bhattarai, U. K. Bhadani, B. K. Biswas, and M. Tripathi. 2008. 'Prevention of hypotension during propofol induction: a comparison of preloading with 3.5% polymers of degraded gelatin (Haemaccel) and intravenous ephedrine', *Nepal Med Coll J*, 10: 16-9.

Dolci, M., P. Frascarolo, D. Hayoz, D. R. Spahn, and J. P. Gardaz. 2011. 'Effect of an intravenous bolus of phenylephrine or ephedrine on skin blood flow during spinal anaesthesia: a randomised, double-blind, controlled study', *Eur J Anaesthesiol*, 28: 226-9.

Eclat_Pharmaceuticals. June 2014. "US Vazculep Package Insert." In.

Foss, V. T., R. Christensen, K. Z. Rokamp, P. Nissen, N. H. Secher, and H. B. Nielsen. 2014. 'Effect of phenylephrine vs. ephedrine on frontal lobe oxygenation during caesarean section with spinal anesthesia: an open label randomized controlled trial', *Front Physiol*, 5: 81.

Ganeshanavar A, Uday AS, Adarsh SE, Ramesh K, Ravi R. 2011. 'Comparison of bolus phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anaesthesia in caesarean section. ', *J Clin Diagn Res*, 5: 948-52.

Gunda, C. P., J. Malinowski, A. Tegginmath, V. G. Suryanarayana, and S. B. Chandra. 2010. 'Vasopressor choice for hypotension in elective Cesarean section: ephedrine or phenylephrine?', *Arch Med Sci*, 6: 257-63.

Iqbal, Muhammad Shakeel; Ishaq, Muhammad; Masood, Ammara; , and Muhammad Zafar Khan. 2010. 'Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during cesarean section', *Anaesth Pain & Intensive Care*, 14: 71-75.

Ishiyama, T., T. Oguchi, T. Iijima, T. Matsukawa, S. Kashimoto, and T. Kumazawa. 2003. 'Ephedrine, but not phenylephrine, increases bispectral index values during combined general and epidural anesthesia', *Anesth Analg*, 97: 780-4.

Kansal, A., M. Mohta, A. K. Sethi, A. Tyagi, and P. Kumar. 2005. 'Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section', *Anaesthesia*, 60: 28-34.

Kasaba, T., M. Yamaga, T. Iwasaki, Y. Yoshimura, and M. Takasaki. 2000. 'Ephedrine, dopamine, or dobutamine to treat hypotension with propofol during epidural anesthesia', *Can J Anaesth*, 47: 237-41.

Kitchen, C. C., P. Nissen, N. H. Secher, and H. B. Nielsen. 2014. 'Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension', *Front Physiol*, 5: 407.

Lecoq, J. P., J. F. Brichant, M. L. Lamy, and J. L. Joris. 2010. 'Norepinephrine and ephedrine do not counteract the increase in cutaneous microcirculation induced by spinal anaesthesia', *Br J Anaesth*, 105: 214-9.

Magalhaes, E., C. S. Goveia, L. C. de Araujo Ladeira, B. G. Nascimento, and S. M. Kluthcouski. 2009. 'Ephedrine versus phenylephrine: prevention of hypotension during spinal block for cesarean section and effects on the fetus', *Rev Bras Anestesiol*, 59: 11-20.

Meersschaert, K., L. Brun, M. Gourdin, S. Mouren, M. Bertrand, B. Riou, and P. Coriat. 2002. 'Terlipressin-ephedrine versus ephedrine to treat hypotension at the induction of anesthesia in patients chronically treated with angiotensin converting-enzyme inhibitors: a prospective, randomized, double-blinded, crossover study', *Anesth Analg*, 94: 835-40, table of contents.

Meng, L., M. Cannesson, B. S. Alexander, Z. Yu, Z. N. Kain, A. E. Cerussi, B. J. Tromberg, and W. W. Mantulin. 2011. 'Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients', *Br J Anaesth*, 107: 209-17.

Meng, L., N. P. Tran, B. S. Alexander, K. Laning, G. Chen, Z. N. Kain, and M. Cannesson. 2011. 'The impact of phenylephrine, ephedrine, and increased preload on third-generation Vigileo-FloTrac and esophageal doppler cardiac output measurements', *Anesth Analg*, 113: 751-7.

Mokhtar, Ali; Sherif, Nadine. 2014. 'Phenylephrine versus ephedrine usage in the management of hypotension-induced spinal anaesthesia in pre-eclamptic patients undergoing caesarean section', *Evidence Based Women's Health Journal*, 4: 55-61.

Moran, D. H., M. Perillo, R. F. LaPorta, A. M. Bader, and S. Datta. 1991. 'Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery', *J Clin Anesth*, 3: 301-5.

Morishita, H., and T. Furukawa. 1975. 'The vascular changes after ephedrine tachyphylaxis', *J Pharm Pharmacol*, 27: 574-9.

Nag, K. 2010. 'One year randomized clinical trial to compare the efficacy of intravenous bolus phenylephrine and ephedrine in maintaining arterial blood pressure during spinal anesthesia in caesarean section (Unpublished dissertation). ', *Jawaharlal Nehru Medical College, Belgaum, Karnataka, India.*

Ngan Kee, W. D., K. S. Khaw, T. K. Lau, F. F. Ng, K. Chui, and K. L. Ng. 2008. 'Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section*', *Anaesthesia*, 63: 1319-26.

Ngan Kee, W. D., K. S. Khaw, B. B. Lee, T. K. Lau, and T. Gin. 2000. 'A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery', *Anesth Analg*, 90: 1390-5.

Ngan Kee, W. D., K. S. Khaw, P. E. Tan, F. F. Ng, and M. K. Karmakar. 2009. 'Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery', *Anesthesiology*, 111: 506-12.

Ngan Kee, W. D., T. K. Lau, K. S. Khaw, and B. B. Lee. 2001. 'Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section', *Anesthesiology*, 95: 307-13.

Ngan Kee, W. D., A. Lee, K. S. Khaw, F. F. Ng, M. K. Karmakar, and T. Gin. 2008. 'A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control', *Anesth Analg*, 107: 1295-302.

Nissen, P., P. Brassard, T. B. Jorgensen, and N. H. Secher. 2010. 'Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension', *Neurocrit Care*, 12: 17-23.

Odagme MT, Fyneface-Ogan S and Mato CN. 2013. 'Prophylactic Infusions of Phenylephrine and Ephedrine during Combined Spinal Epidural Anaesthesia for Caesarean Section: A Comparative Study', *Journal of Anesthesia & Clinical Research*, 4.

Pennekamp, C. W., R. V. Immink, F. L. Moll, W. F. Buhre, and G. J. de Borst. 2012. 'Differential effect of phenylephrine and ephedrine on cerebral

haemodynamics before carotid cross-clamping during carotid endarterectomy', *Br J Anaesth*, 109: 831-3.

'Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology'. 2016. *Anesthesiology*, 124: 270-300.

Prakash, S., V. Pramanik, H. Chellani, S. Salhan, and A. R. Gogia. 2010. 'Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomised study', *Int J Obstet Anesth*, 19: 24-30.

Puri, N.; Talwar, A. 2010. 'Comparative Study of Ephedrine and Mephertermine in Treatment of Hypotension in Patients Undergoing Elective Trans Urethral Resection Prostate (TURP)', *Journal of Bangladesh College of Physicians and Surgeons*, 28: 10-16.

Ramanathan, S., and G. J. Grant. 1988. 'Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section', *Acta Anaesthesiol Scand*, 32: 559-65.

Rehman, Abdul; Baig, Harris; Rajput, M. Zameer; Zeb, Huma. 2011. 'Comparison of prophylactic ephedrine against prnephedrine during spinal anesthesia for caesarian sections', *Anaesthesia, Pain & Intensive Care*, 15.

Saravanan, S., M. Kocarev, R. C. Wilson, E. Watkins, M. O. Columb, and G. Lyons. 2006. 'Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section', *Br J Anaesth*, 96: 95-9.

Simin, A;Zahra, F; Pouya, H.M.; Reza, T. 2012. 'Comparison the effect of ephedrine and phenylephrine in treatment of hypotension after spinal anesthesia during cesarean section', *Open Journal of Obstetrics and Gynecology*, 2: 192-96.

Supervalu_Inc. October 2014. 'EQUALINE NASAL DECONGESTANT NON DROWSY MAXIMUM STRENGTH Product Packaging '.

Taguchi, N., T. Nishikawa, S. Inomata, M. Taguchi, S. Yamashita, and H. Naito. 1996. 'Hemodynamic effects of intravenous ephedrine in infants and children anesthetized with halothane and nitrous oxide', *Anesth Analg*, 82: 568-73.

Taivainen, T. 1991. 'Comparison of ephedrine and etilefrine for the treatment of arterial hypotension during spinal anaesthesia in elderly patients', *Acta Anaesthesiol Scand*, 35: 164-9.

Tanaka, M., and S. Dohi. 1994. '[The effects of ephedrine and phenylephrine on arterial partial pressure of oxygen during one-lung ventilation]', *Masui*, 43: 1124-9.

Thomas, D. G., S. C. Robson, N. Redfern, D. Hughes, and R. J. Boys. 1996. 'Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section', *Br J Anaesth*, 76: 61-5.

Turkoz, A., T. Togal, R. Gokdeniz, H. I. Toprak, and O. Ersoy. 2002. 'Effectiveness of intravenous ephedrine infusion during spinal anaesthesia for caesarean section based on maternal hypotension, neonatal acid-base status and lactate levels', *Anaesth Intensive Care*, 30: 316-20.

Vercauteren, M. P., H. C. Coppejans, V. H. Hoffmann, E. Mertens, and H. A. Adriaensen. 2000. 'Prevention of hypotension by a single 5-mg dose of ephedrine during small-dose spinal anesthesia in prehydrated cesarean delivery patients', *Anesth Analg*, 90: 324-7.

Videira, R. L. R.; Lousada, M. C.; Neto, M. Brandao. 2000. 'Prophylactic intravenous ephedrine during spinal anaesthesia for Caesarean section: bolus or infusion?', *European Journal of Anaesthesiology*, 17.

West-Ward_Pharmaceuticals. December 2012. "US Phenylephrine Hydrochloride Package Insert." In.

Wright, P. M., M. Iftikhar, K. T. Fitzpatrick, J. Moore, and W. Thompson. 1992. 'Vasopressor therapy for hypotension during epidural anesthesia for cesarean section: effects on maternal and fetal flow velocity ratios', *Anesth Analg*, 75: 56-63.

Xu, Bo; Wang, Fengmei. 2013. 'Effects of ephedrine and phenylephrine on the correction of hypotension in the cesarean sections under subarachnoid anesthesia', *HealthMED*, 7: 2607-12.

Yousefshahi, Fardin ; Tanha, Fatemeh Davari; Kaveh, Mahbod; Hamidian, Roghayeh; Barkhordari, Khosro. 2010. 'The Effect of Ephedrine on Fetal Outcome in Treatment of Maternal Hypotension Caused by Spinal Anesthesia During Cesarean Section', *Journal of Family and Reproductive Health*, 4: 149-54.

Note:
Ngan Kee et al. 2008a is the following publication: Ngan Kee, W. D., A. Lee, K. S. Khaw, F. F. Ng, M. K. Karmakar, and T. Gin. 2008. 'A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control', Anesth Analg, 107: 1295-302.

Ngan Kee et al. 2008b is the following publication: Ngan Kee, W. D., K. S. Khaw, T. K. Lau, F. F. Ng, K. Chui, and K. L. Ng. 2008. 'Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section*', Anaesthesia, 63: 1319-26.

Meng et al. 2011a is the following publication: Meng, L., M. Cannesson, B. S. Alexander, Z. Yu, Z. N. Kain, A. E. Cerussi, B. J. Tromberg, and W. W. Mantulin. 2011. 'Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients', Br J Anaesth, 107: 209-17.

Meng et al. 2011b is the following publication: Meng, L., N. P. Tran, B. S. Alexander, K. Laning, G. Chen, Z. N. Kain, and M. Cannesson. 2011. 'The impact of phenylephrine, ephedrine, and increased preload on third-generation Vigileo-FloTrac and esophageal doppler cardiac output measurements', Anesth Analg, 113: 751-7.

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

/s/

MARY A LUCKETT
04/28/2016

RIGOBERTO A ROCA
04/28/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208289 **Applicant: Flamel Ireland Limited** **Stamp Date: June 30, 2015**

Drug Name: Akovaz (ephedrine sulfate injection, USP) **NDA Type: 505 (b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505 (b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?			X	All references are to published literature.
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)				The Applicant provided literature in which ephedrine as the (-)enantiomer is identified .
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:	X			Dosage determined from literature, although unable to find justification for

Reference ID: 3812165

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Arms: Location in submission:				maximum daily dose. A request for information will be communicated to the Applicant.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: N/A Pivotal Study #2 Indication: N/A			X	
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

Reference ID: 3812165

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The Applicant attempted to obtain study protocols and clinical data sets for published literature to be used to support ephedrine's efficacy, but no additional information was able to be obtained.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Agreed iPSP dated 7/13/2015. Waiver for those less than (b) (4) years-old. (b) (4) to 16-year-olds will be studied for safety and PK/PD.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3812165

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	Flamel has concluded "that the studies published by foreign and U.S. investigators were conducted according to the principals of Good Clinical Practice." (Source: Applicant's Summary of Clinical Efficacy page 9) Study authors of publications cited for determination of efficacy obtained Informed Consent and described an IRB or ethics committee. An exception is study author Pennekamp, who indicated that "ethical approval was required and provided for the study." (Source: Applicant's Summary of Clinical Efficacy page 11)

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We are unable to find justification for the maximum daily dose of ephedrine in your submission. Provide justification for the maximum daily dose of ephedrine or indicate where it can be found in your submission.

Reference ID: 3812165

2. We noted a variety of adverse events with ephedrine in the FAERS data that you submitted that were not included in the proposed labeling. How did you determine which adverse events to leave out of the proposed labeling?

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3812165

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

/s/

MARY A LUCKETT
08/27/2015

RIGOBERTO A ROCA
08/27/2015