CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review Memo

Date	April 7, 2014
From	Christopher D. Breder, MD PhD Clinical Team Leader, Anesthetic Drugs CDER/OND/ODEII/DAAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supp #**	NDA # 204300 Supp # 6
Proprietary / Established (USAN) names	Vazculep® phenylephrine hydrochloride injection
Dosage forms / strength	Solution for injection / 10 mg/ml
Proposed Indication(s)	1. Treatment of hypotension during anesthesia 2. [redacted] (b) (4)
Recommended:	1. Treatment of hypotension during anesthesia – Approval 2. [redacted] (b) (4)

1. Introduction to Review

Éclat Pharmaceuticals re-submitted a New Drug Application (NDA) for phenylephrine hydrochloride (PHE) injection 1% (10 mg/mL), USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The proposed indications are for the treatment [redacted] (b) (4) of hypotension during anesthesia, as a bolus or as a continuous infusion.

The drug product is a sterile, nonpyrogenic solution of PHE formulated in one strength, 10 mg/mL, and it is intended for dilution and administration via intravenous route. Three fill volumes are proposed for marketing: 1 mL, 5 mL, and 10 mL, with 5 mL and 10 mL vials designated for pharmacy distribution only.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Three meetings were held between the Applicant (then Sponsor of IND 113044) and the Division.

- The first meeting was held on November 17, 2011 (minutes from 12/19/2011). In this meeting, the Division commented on issues related to Dosing and Administration.
- The second meeting was an End-of-Phase 2 (EOP2) meeting held on September 27, 2012 (minutes from 10/29/2012). In this meeting, the potential indications and the literature database were discussed. The Division noted that

[redacted] (b) (4)

(b) (4)

Issues surrounding regulatory aspects of submitting a505 (b)(2) application were also discussed.

- The third meeting, planned for January 30, 2013, was cancelled after the Sponsor received preliminary comments. These comments discussed issues related to the 505(b)(2) filing strategy the Applicant had planned for your New Drug Application (NDA.) and also issues with respect to the choice of indication.

The Applicant's original NDA submission was received on February 8, 2013.

The Agency issued a Refuse to File letter to the Applicant (deficiencies in construct of Integrated Summary of Efficacy and Integrated Summary of Safety), on April 5, 2013. A meeting was held June 13, 2013 (minutes from September 11, 2013) that dealt primarily with the format of the planned resubmission.

Current Submission
The current application is a re-submission (submitted June 28, 2013) of the original application with revisions to Integrated Summary of Efficacy and Integrated Summary of Safety sections.

This 505(b)(2) NDA submission is based on the literature in adult population. Therefore, the Applicant did not make any reference to any listed product for PHE Injection, USP, 1%. The Applicant intends to rely solely on literature to support the non-clinical, clinical pharmacology, clinical safety and efficacy of the proposed PHE injection. The Applicant stated, however, that they are referencing information included in DMF (b) (4) for PHE hydrochloride and the USP monograph for PE injection.

3. CMC/Microbiology/Device

3.1. General product quality considerations

The approval recommendation by the CMC team is contingent upon the satisfactory resolution of the remaining CMC issues. The major issues include the following:

- Data documenting the absence of potential leachable, (b) (4) to be submitted by April 2, 2014, per agreement provided on March 19, 2014.

The Applicant discussed preliminary results for the content of potential [(b) (4)] leachable in communication dated March 19, 2014, indicating that stability samples stored for 22 months at 30°C have [(b) (4)]. Applicant agreed to provide final test results and brief method validation in NDA amendment by April 2, 2014. The preliminary negative results for the potential [(b) (4)] leachable and the provided agreement alleviate the CMC safety concerns regarding this leachable. At this point ONDQA does not consider it necessary to include the testing for leachables in the drug product stability protocol.

- Specifications for the content of sodium metabisulfite during shelf-life of the product as described in PMC #1.
- Tightening of the tentative release specifications for the content of sodium metabisulfite as described in PMC #2.

The proposed PMCs are considered sufficient to address the potential safety and quality aspects associated with the level of sodium metabisulfite [(b) (4)] in the drug product formulation. Although most likely there is a minimum level of the [(b) (4)] required to assure the strength of the drug product, the stability of the formulation is indirectly controlled by the acceptance criteria for pH, individual impurities and total impurities.

[(b) (4)]. In addition, a report will be provided to the Agency documenting the changes occurring in the level of sodium metabisulfite throughout the life-time of the drug product, along with a study documenting a minimum level of sodium metabisulfite required to sustain the [(b) (4)] function.

- Special stability report to be submitted in each Annual Report. It will include analysis of instability trends, including results for all stability-indicating attributes, including the requested data [(b) (4)] level, storage orientation), as described in Agreement #1.

The stability data submitted to this NDA include results for 9 registration batches ([(b) (4)] for samples stored in one orientation [(b) (4)] for 18 months. Data do not include content of [(b) (4)] (see PMCs) and indicate different instability trends (pH, impurities) for small fill vials (1 mL and 5 mL) with large head volume in comparison to the 10 mL fill with small head volume, most likely due to the [(b) (4)]. As a result, the impurity levels and pH are [(b) (4)] for different product fills after storage; however the results are within specification limits. Also, no report or data documenting the preferred-for-storage orientation for the product is currently available.

The Agreement to include additional storage orientation for stability samples and to provide analysis of the instability trends for the commercial products in each annual report is adequate to monitor the quality of the proposed-for-marketing product and sufficiently addresses the CMC concerns.

The Microbiology evaluation of [redacted] and process controls and validation was performed by the OPS Microbiology Team and adequate-for-approval status is recommended in the review dated March 12, 2014, by Dr. S. Langille.

3.1.1. Facilities review/inspection

The Evaluation Establishment Request (EER) was submitted and the final recommendation from the Office of Compliance is pending. An acceptable recommendation is available for the drug product manufacturing facility [redacted] and two testing sites. However, the results of inspection at the drug substance manufacturing site owned [redacted] (current status: Withhold) are under evaluation by the Office of Compliance.

3.2. Other notable issues

No other notable issues.

3.3. Postmarketing Requirements / Commitments/ Agreements

Two Post-Marketing Commitments (PMC) pertaining to specifications for the content of sodium metabisulfite [redacted], and an agreement pertaining to submission of a special stability assessment report, are recommended by the CMC team, as described below.

Post-Marketing Commitments

(PMC #1)
Éclat commits to establish final, data-based [redacted] acceptance criteria for the content of sodium metabisulfite in the drug product, [redacted]

(PMC #2)
Éclat commits to tighten the currently proposed tentative release acceptance criteria ([redacted] for the content of sodium metabisulfite in the drug product, [redacted].

Agreement

(Agreement #1)
Éclat agrees to provide annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches, as described in NDA amendment dated March 11, 2014. The analysis will be focused on different instability trends for smaller fill volumes with a large head space (i.e., 1 mL and 5 mL) in comparison to the 10 mL fill volume with a small head space. Also, Éclat agrees to submit an evaluation of trends in

sodium metabisulfite content in the context of changes in pH and impurity levels as well as analyze the impact of storage orientation on instability trends. The first report is scheduled to be submitted by April 2015, and it will contain analysis of 6 months stability data collected at the accelerated (40 ± 2 °C/75% ± 5% RH) and at long-term (25 ± 2°C/60% ± 5% RH) storage conditions for commercial manufacturing.

3.4. Recommendation and Conclusion on Approvability

The application is approvable from the CMC perspective providing that the Applicant addresses satisfactorily the remaining CMC agreement (submission data for leachables and an acceptable recommendation is provided by the Office of Compliance (OC) regarding the status of the manufacturing and testing facilities for this product.

4. Nonclinical Pharmacology/Toxicology

4.1. Background and Review Strategy

There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application.

In several meetings with the Applicant prior to submission of the NDA, the Division noted that if there is adequate clinical experience with the drug product, no general toxicology studies would be required to support the NDA. The Applicant was requested to provide a literature review to address the potential for genotoxicity, carcinogenicity, and reproductive and developmental toxicity of PHE to inform product labeling. If upon review, these data were deemed inadequate to inform labeling, further studies may be required to be completed post-approval.

4.2. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

Findings in the published literature have demonstrated that PHE increases blood pressure by binding to and stimulating alpha 1-adrenergic receptors.

There are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants have been adequately qualified for safety. The container closure system has been adequately qualified for safety.

4.3. Carcinogenicity

Carcinogenicity studies were conducted in rats and mice treated with PHE via their diet. Daily doses approximately 50 mg/kg (300 mg/m2) in rats and 270 mg/kg (810 mg/m2) in mice were not deemed carcinogenic following two years of treatment.

4.4. Reproductive toxicology

The nonclinical review noted reproductive toxicology studies in normotensive rabbits were conducted to evaluate the effect of PHE administration during various stages of gestation. These studies[1] indicate that subcutaneous administration of PHE to pregnant rabbits (0.33 mg/kg, TID) resulted in premature labor onset, decreased litter weights, increased neonate deaths and still births, and histopathology findings in the placenta such as necrosis, thickened vascular walls, and narrowed lumina. Studies in normotensive pregnant sheep demonstrated that PHE increases blood pressure and produces reflex bradycardia in both the ewe and the fetus and decreases uterine blood flow at doses that were slightly greater than the upper dosing range in humans. PHE infusion decreased uterine blood flow up to 42%. These findings, in normotensive animals, suggest the potential for risk and should be included in the drug product labeling at this point. However, none of the studies are deemed adequate by current standards, and the results from studies in normotensive animals may not reflect clinical conditions if the drug is used only to treat hypotension and restore blood pressure to normal. (b) (4) Based on the limited data in the literature, the full reproductive and developmental toxicology study battery of studies are recommended as PMRs. Careful design of these studies to include assessment of clinically relevant conditions, if possible, should be discussed with the Applicant.

4.5. Other notable issues

No other notable issues

4.6. Postmarketing Requirements / Commitments/ Agreements

Based on the data submitted to date, the following studies are recommended as post-marketing requirements (PMRs), should this NDA be approved during this cycle:

PMR 1
Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

PMR 2
Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

PMR 3
Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

PMR 4

[1] Specifically pregnant rabbits were treated from Gestation Day (GD) 3 to GD 10 or parturition, GD 7 to parturition, or GD 12 to parturition. Collectively this dosing period covers the period of organogenesis (typically GD 6-18 in the rabbit).

Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

A teleconference will be conducted after the submission of this memo between the Division and the Applicant to discuss the PMRs and their associated timelines.

4.7. Recommendation and Conclusion on Approvability

From a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with the recommended PMRs and pending agreement on labeling.

5. Clinical Pharmacology/Biopharmaceutics

5.1. Background and Review Strategy

The Applicant did not conduct any pharmacokinetic drug-drug interaction studies. Instead they are relying on information that can be found in the literature and other sources to support the proposed labeling. Since the Applicant's as well as marketed products are a parenteral product intended for intravenous administration (bioavailability of this intravenous drug product is self-evident) and it seems that formulations do not contain ingredients that would affect the bioavailability or pharmacokinetics of PHE, it appears that the submitted literature information will be sufficient to meet the clinical pharmacology requirement.

5.2. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Following an intravenous PHE infusion, the PHE concentration-time curve exhibited biphasic decline, as observed by an initial rapid distribution followed by relatively slow elimination. The reported average steady state volume of distribution (Vss) and elimination half-life were 340 L (range 184 to 543 L) and 151 minutes (2.51 h based on β-phase), respectively. The observed distribution phase was rapid (less than 5 minutes based on α-phase).

PHE is primarily metabolized in the liver and eliminated in the urine. PHE is metabolized primarily by monoamine oxidase and sulfotransferase. Based on 3H-PHE intravenous administration, approximately 86% (approximately 80% of the administered dose was eliminated within first 12 h) of the intravenously administered dose was recovered in the urine within 48 h. The excreted unchanged drug (i.e., parent PHE) was 16% of the dose in the urine at 48 h post intravenous administration. There are two major metabolites with approximately 57 and 8% of the administered dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active.

5.3. Drug-drug interactions

The majority of studies described a pharmacodynamic response (e.g., blood pressure, mean arterial pressure) of PHE as variety of medications may affect the sensitivity of tissue α-

adrenoreceptors and either increase or decrease vasopressor effect of PHE. An exception to above is of monoamine oxidase inhibitors (affecting PHE's metabolism), which may increase the systemic PE concentrations, due to the fact that PHE is primarily metabolized by monoamine oxidase. A review of the literature revealed that reserpine has also been reported to affect PHE pharmacokinetics through inhibition of the vesicular monoamine transporter.

A variety of medications may affect the sensitivity of tissue α-adrenoreceptors and either increase or decrease vasopressor effect of PHE. The following class of drugs may increase vasopressor activity of PHE and lower dose of PHE may be needed when coadministered: monoamine oxidase inhibitors, tricyclic antidepressants, alpha-adrenergic agonists, oxytocic (e.g., oxytocin), and, angiotensin agents (e.g., aldosterone). The following class of drugs may decrease vasopressor activity of PHE and higher dose of PHE may be needed when coadministered: alpha-adrenergic antagonists (e.g., doxazosin), phosphodiesterase type 5 inhibitors (e.g., sildenafil), adrenergic receptor antagonists (e.g., labetalol), calcium channel blockers (e.g., nifedipine), benzodiazepines (e.g., midazolam, lorazepam), and, angiotensin converting enzyme inhibitors (e.g., quinapril, enalapril).

In addition, the following moieties are identified as possible agonist/antagonist for PHE; atropine, steroids, norepinephrine transporter inhibitors and methylergonovine maleate may enhance PHE's pressor effect and lower dose of PHE may be needed. However, higher dose of PHE may be needed when centrally acting sympatholytic agents (e.g., reserpine, guanfacine) as they may decrease the PHE's pressor effect.

5.4. Pathway of Elimination

Renal Impairment

In patients with end stage renal disease (ESRD), dose-response data indicate increased responsiveness to PHE. It is suggested that patients with renal impairment may start with lower than recommended dose, and dose adjustment may be needed based on the patient's response to the product

Hepatic Impairment

In contrast to renal impairment, the literature suggests that in patients with liver cirrhosis, dose-response data indicate decreased responsiveness to PHE. Higher doses of PHE may be required in liver cirrhosis patients (Child-Pugh B or C), and dose adjustment may be needed based on the patient's response to the product.

5.5. Demographic interactions/special populations

Age

Information regarding use of PHE hydrochloride in the elderly population varies widely. White et al. 1999 reported that, in a baroreceptor study, a positive correlation of increased sensitivity to PHE's pressor effects for older adult subjects >50 years (range 5-73 years) compared to younger subjects (<40 years, range 21-40). However, Schwinn and Reves (1989)

reported a negative correlation between age and PHE based on measurements of systemic vascular resistance response to pressor infusion[2].

Race

Stein et al. (2000) studied the sensitivity to α-vasopressor and β-vasodilator in healthy normotensive young black and white subjects[3]. Forearm blood flow was measured with strain gauge plethysmography after intra-arterial administration of PE (1.25 to 20 mcg/min) or isoproterenol, after application of lower-body negative pressure, and after a cold pressor test. PHE decreased forearm blood flow more in healthy young black subjects than in healthy young white subjects (Figure 11). At the 10 mcg/min PE dose, PE decreased blood flow measured at baseline by a mean of 58.0 ± 2.5% in healthy young black subjects vs. 26.6 ± 6.0% in healthy young white subjects.

Gender

Wolzt et al. (1995) conducted a double-blind, randomized cross-over trial to compare the PHE responses in healthy male and female volunteers[4]. There was a significant gender difference for several of the hemodynamic parameters (e.g., systolic and diastolic blood pressures, pulse pressure, pulse rate) under baseline conditions; however, no difference in responsiveness to PE was reported.

Drug-Disease Interactions

White et al. (1999) evaluated PE responsiveness in patients differing by age and by the presence or absence of pre-existing hypertension (young normotensive, young hypertensive, old normotensive, old hypertensive)[5]. Compared to young normotensives, the older normotensive subjects and both young and older hypertensive subjects exhibited a similar increase in systolic blood pressure in response to PHE

Grassi et al. (2000) evaluated the effects of obesity-related hypertension on adrenergic and reflex abnormalities (lean normotensive and hypertensive subjects, obese normotensive and hypertensive subjects)[6]. Blood pressure values were higher in lean and obese hypertensive subjects compared to lean and obese normotensive subjects. The authors suggested that obesity and hypertension have additive effect on blood pressure. Compared with lean normotensive control subjects, the reflex responses were less in the obese normotensive and lean hypertensive subjects; a further reduction was observed in obese hypertensive subjects. The

[2] Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Schwinn DA, Reves JG. Anesth Analg. 1989 May;68(5):571-8.
[3] Increased vascular adrenergic vasoconstriction and decreased vasodilation in blacks. Additive mechanisms leading to enhanced vascular reactivity. Stein CM, Lang CC, Singh I, He HB, Wood AJ. Hypertension. 2000 Dec;36(6):945-51
[4] Comparison of non-invasive methods for the assessment of haemodynamic drug effects in healthy male and female volunteers: sex differences in cardiovascular responsiveness. Wolzt M, Schmetterer L, Rheinberger A, Salomon A, Unfried C, Breiteneder H, Ehringer H, Eichler HG, Fercher AF. Br J Clin Pharmacol. 1995 Apr;39(4):347-59
[5] Effects of age and hypertension on cardiac responses to the alpha1-agonist phenylephrine in humans. White M, Fourney A, Mikes E, Leenen FH. Am J Hypertens. 1999 Feb;12(2 Pt 1):151-8.
[6] Adrenergic and reflex abnormalities in obesity-related hypertension. Grassi G, Seravalle G, Dell'Oro R, Turri C, Bolla GB, Mancia G. Hypertension. 2000 Oct;36(4):538-42.

authors concluded that an association between obesity and hypertension triggers sympathetic activation and impairment in baroreflex cardiovascular control.

5.6. Thorough QT study or other QT assessment

No information was submitted to characterize PHE's effect on QT. There did not seem to be a signal from the literature reviewed by Dr. Jiang (see Section 7.2.2.5) or from the postmarketing surveillance investigation provided by Drs. Argual and Gilbert (see Section 9). Inasmuch as the Clinical Pharmacology group did not believe this to be a deficiency requiring further study before or after approval, I concur with this position considering the long clinical use without a known, related safety signal.

5.7. Other notable issues *(resolved or outstanding)*

No other notable issues.

5.8. Postmarketing Requirements / Commitments/ Agreements

Not applicable.

5.9. Recommendation and Conclusion on Approvability

From a clinical pharmacology perspective, the information submitted in the NDA is Acceptable [for approval], pending agreement on the labeling language.

6. Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Relevant Background and Review Strategy

Dr. Tim Jiang, MD, a Medical Officer (MO) in DAAAP reviewed the safety and efficacy for both indications. In both his review and in my CDTL memo, the findings and issues for the efficacy of the two indications are discussed separately.

The Applicant submitted 16 publications to support a finding of efficacy for treatment of hypotension during anesthesia. No placebo controlled studies were identified. Most studies are active-controlled with ephedrine (an unapproved product) as the active comparator.

From the ISE, the suggested primary endpoint by the Applicant for the treatment indication is "*…to reverse clinically relevant hypotensive effects of anesthesia, in many instances defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline.*"

(b) (4)

(b) (4)

7.1.2. Dose identification/selection and limitations

Studies described in the literature[7], standard textbooks[8], and practice guidelines[9] suggest that PHE dose is often titrated to achieve the desired effect of maintaining or increasing the patient's blood pressure during surgery. This often involves repeated administration. The differences in PHE dose(s) needed in a patient may depend on a patient's sensitivity to PHE and is based on patient factors such as the heart rate, baseline blood pressure, volume status, cardiac history to name just a few. As such, the Applicant proposed doses of PHE ranging from 40 mcg to 100 mcg every 1-2 minutes as needed, not to exceed 200 mcg, and, 10 mcg /min to (b) (4) mcg /min, not to exceed 200 mcg /min. based on the literature evidence extracted from Dr. Lee's review, for bolus (**Table 1**) and infusion (**Table 2**), respectively and from additional clinical literature reviewed by Dr. Jiang.

[7] e.g., Vasopressor use in adult patients. Ferguson-Myrthil N.Cardiol Rev. 2012 May-Jun;20(3):153-8
[8] Miller RD et al, (editors) : Anesthesia (6th ed.), New York, 2005, Churchill Livingstone.
[9] Practice Guidelines for Obstetric Anesthesia Anesthesiology 2007; 106:843–63

Table 1 Blood Pressure Response to PHE bolus injection

Reference	Patient population	PE Dose	Blood Pressure Just Prior to PE Application	Blood Pressure After PE Application	Δ BP	Time after PE Dose
Goertz et al. 1993b	Coronary artery disease and valvular aortic stenosis	1 µg/kg (~72 µg[a])	MAP 69-71mm Hg	MAP 94-99 mm Hg	23-30 mm Hg	60 sec
Dyer et al. 2008b	Cesarean delivery with spinal anesthesia	50-100 µg, repeated every minute as needed	MAP 91 mm Hg	MAP 108 mm Hg	17 mm Hg	Within 24 to 40 seconds of dosing
Goertz et al. 1993a	Elective minor abdominal or orthopedic surgery	2 µg/kg (~148 µg[c])	61 mm Hg	83 mm Hg	22 mm Hg	30 sec
Ishiyama et al. 2003	Elective surgery under combined general and epidural anesthesia	2 µg/kg (~112 µg[d])	61 mm Hg	80 mm Hg	~19 mm Hg	2.5 min
Dyer et al. 2009	Cesarean delivery with spinal anesthesia	80 µg	72.8 mm Hg	98.5 mm Hg	25.7 mm Hge	61.8 sec
Alahuhta et al. 1992	Cesarean delivery with spinal anesthesia	100 µg bolus (followed by 100 µg bolus)	SAP 109 mm Hg	SAP 115 mm Hg	6 mm Hg	-

[a] µg/kg x mean weight 69-75 kg = 69-75 µg
[b] Blood pressure response was measured after multiple PE doses
[c] 2 µg/kg x mean patient weight of 74 kg = 148 µg
[d] 2 µg/kg x mean patient weight of 56 kg = 112 µg
[e] Based on mean MAP values pre and post-vasopressor

Source: Table 7, Clinical Pharmacology review

Table 2 Blood Pressure Response to PHE infusion

Table 8: Blood pressure response to phenylephrine (PE) intravenous infusion with or without initial bolus injection (SBP: systolic blood pressure; SAP: systolic arterial pressure; MAP: mean arterial pressure)

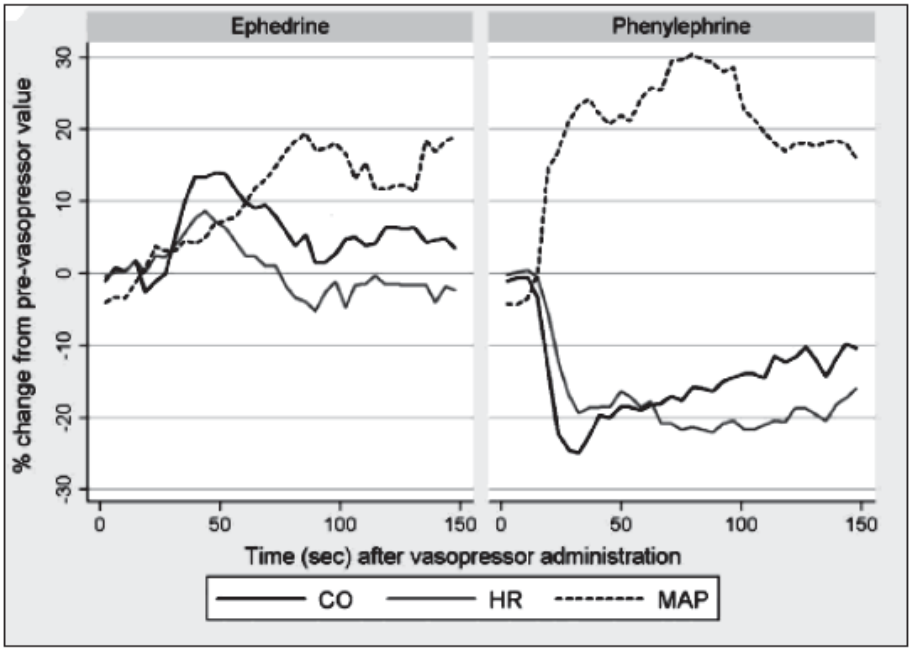
Reference	Patient population	PE Dose	Baseline MAP	Post-dose MAP	MAP Response	Time of Post- dose Evaluation
Nygren et al. 2006	Coronary artery bypass grafting surgery	0.50 ± 0.22 µg/kg/min (range, 0.21± 0.94 µg/kg/min) ~35 µg/min	68 ± 5 mm Hg	92 ± 4 mm Hg	24 mm Hg	NA
Brooker et al. 1997	Elective surgery with tetracaine spinal	40 µg bolus (followed by infusion with 0.5 µg/kg/mina	MAP 82 mm Hg	MAP 100 mm Hg	18 mm Hg	NA

[a] Calculated from mean weight of population studied in Brooker et al. (1997)

Source: Table 7, Clinical Pharmacology review

The onset and duration of action (blood pressure and heart rate) of PE are rapid. Time course of PE effect on mean arterial pressure (MAP) is shown in Figure 4. The figure shows that the onset of action is immediate and lasts perhaps minutes after the injection. Mean arterial pressure (dashed line) shows a significant increase within seconds, peak effects within approximately one minute, followed by decline towards baseline. The figure suggests that PE may be dosed few minutes as needed to maintain target blood pressure.

Figure 1 Time course of PHE effect



Source: Figure 4, Clinical Pharmacology Review

7.1.3. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The following subsections of 7.1.3. describe the evidence for PHE's effect on increasing blood pressor in the treatment (b) (4) indications and is generally organized according to the different anesthesia scenarios (neuraxial versus general anesthesia), administered by different regimen (bolus versus infusion), and in different population's (obstetrical versus non-obstetrical).

Treatment of Hypotension Indication

Literature providing data on the effect of PHE for the indication of the treatment of hypotension described a variety of procedures, including CABG, valvular heart surgery and elective abdominal, orthopedic, urologic, and gynecologic procedures. In addition, this collection of studies shows the international experience in using PHE to treat anesthesia-induced hypotension, with three originating from investigators in the US, two in the UK and Canada, five in the EU, four in Asia, and one each in South America and Africa.

Hypotension was usually defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline.

In this section, I will review the evidence summarized by the Applicant and reviewed by Dr. Jiang. I have organized this section by anesthesia type (general versus neuraxial), method of administration (bolus or infusion) and population (obstetrical versus non-obstetrical). While this could potentially give rise to 9 groups, some of these combinations are not represented in the literature because they do not occur frequently, e.g., general anesthesia is not typically used in the obstetrical population.

<u>General Anesthesia-Bolus Administration of PHE – Non-obstetrical Population</u>
Three papers were submitted that described the administration of PHE by bolus for the treatment of hypotension associated with a general anesthetic in the non-obstetrical population.

The reference by Schwinn and Reves[10] was particularly illustrative regarding dose selection. **Table 3** demonstrates the change in Mean Arterial Pressure in mmHg (MAP) following 50, 100, 150, and 200 mcg. Dose of 150 and 200 mcg do not result in a significant incremental increase in blood pressure above the lower doses.

[10] Schwinn and Reves, (1989)

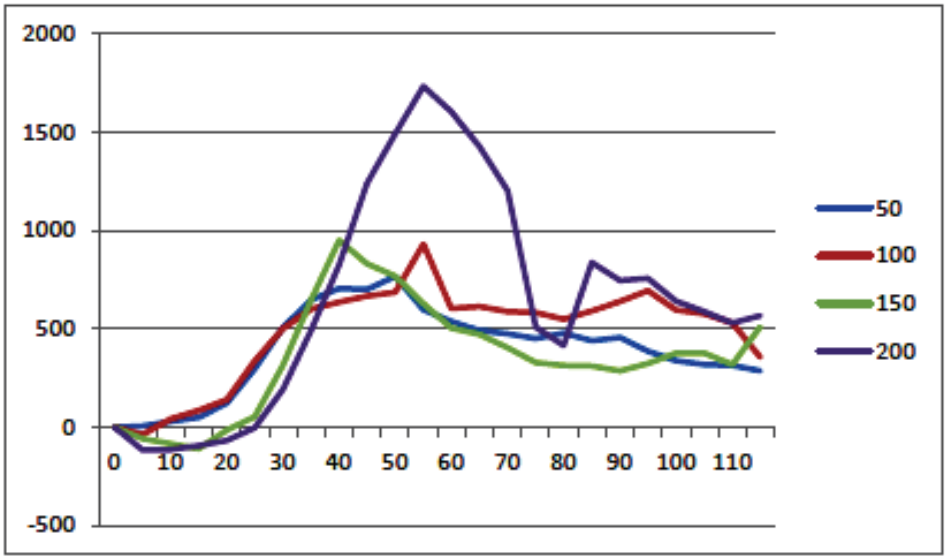
Table 3 Change in MAP by Dose of PHE

	Change in MAP (mm Hg)								
	Time After Bolus PE Injection (seconds)								
PE Dose (µg)	10	20	30	40	50	60	70	80	90
50 (n = 24)	-0.5 ±0.5	2.6 ±1.0	9.7 ±1.8	11.6 ±2.1	10.9 ±1.9	8.8 ±2.0	7.0 ±2.2	7.9 ±2.0	8.0 ±1.9
100 (n = 17)	0.9 ±1.0	5.6 ±1.7	12.6 ±1.8	14.6 ±2.2	15.6 ±2.6	13.6 ±2.8	13.7 ±2.8	13.1 ±2.8	12.9 ±3.1
150 (n = 3)	-1.0 ±0.6	1.0 ±4.6	8.7 ±6.0	14.7 ±2.4	13.7 ±0.7	12.0 ±1.5	10.3 ±2.0	9.3 ±2.0	8.7 ±1.8
200 (n = 6)	0.7 ±1.6	3.7 ±3.3	9.5 ±2.8	16.0 ±1.9	18.0 ±1.5	13.8 ±2.2	13.3 ±2.6	13.6 ±2.4	14.8 ±2.4

Source: Table 4, Clinical Pharmacology review

The 200 mcg dose increases the systemic vascular resistance more significantly than the other doses (**Figure 2**). This could have the untoward effect of increasing cardiac work or decreasing cardiac output suggesting that there is an optimal dose range for achieving an acceptable balance between the therapeutic value and adverse systemic effects. An initial dose of 50 or 100 mcg may provide the needed pressor effect and if insufficient, may be redosed after the resulting blood pressure is evaluated.

Figure 2 SVR Dose Response to PHE vs. Time post dose by Dose



*PE doses were 50, 100, 150 and 200 µg bolus dose

Neuraxial Anesthesia-Bolus Administration of PHE – Obstetrical Population

Eight papers were submitted that described the administration of PHE by bolus for the treatment of hypotension associated with neuraxial anesthesia in the obstetrical population.

The paper by George et al.[11], demonstrated that a 100 or 120 mcg bolus was usually successful in reversing a 20% drop in systolic blood pressure (SBP) or SBP < 90 mm Hg within 1 minute. No hypertensive episodes were observed in the study population although bradycardia was noted at 140 mcg.

Table 4 Probability of Reversing Hypotensive Episodes Associated with Neuraxial Anesthesia by Dose by Bolus PHE in the Obstetrical Population

Dose (µg)	Successes (n)	Trials (n)	Probability (Observed)	Probability (PAVA[a])
80	1	3	0.33	0.33
100	13	17	0.76	0.76
120	10	11	0.91	0.87
140	4	5	0.80	0.87
160	6	7	0.86	0.87
180	2	2	1.00	1.00

[a] PAVA = pooled adjacent violators algorithm

Source – Table 7, Primary Clinical review

Similar results were described in other references reviewed by Dr. Jiang.

General Anesthesia-Infusion of PHE – Non-Obstetrical Population

Three papers submitted that described the administration of PHE by infusion for the treatment of hypotension associated with general anesthesia in the non-obstetrical population.

Data from Nygran et al.,[12] (2006) and Kwak et al.,[13] (2002) were presented in Section 7.1.2. These studies used infusion rates 0.21-0.94 mcg/kg/min and resulted in increases to as much as 50% greater than baseline. These data emphasize the importance of initiating treatment at a low rate and titrating to the desired blood pressure. Neither paper provided detail about the relationship of dose to the decrease in heart rate or the increase in SVR or pulmonary artery pressure demonstrated by PHE.

Neuraxial Anesthesia-Infusion of PHE – Obstetrical Population

One paper was submitted evaluating the effect of PHE administered by infusion for hypotension associated with neuraxial anesthesia in the obstetrical population. Alahuhta et al.

[11] Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. George RB, McKeen D, Columb MO, Habib AS. Anesth Analg. 2010 Jan 1;110(1):154-8.
[12] Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs. phenylephrine. Nygren A1, Thorén A, Ricksten SE. Crit Care Med. 2006 Mar;34(3):722-9.
[13] The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. Kwak YL, Lee CS, Park YH, Hong YW. Anaesthesia. 2002 Jan;57(1):9-14.

studied the effect of a 100 mcg bolus followed by 16.7 mcg/min infusion. This treatment was able to increase the SBP and DBP (column 3 in **Table 5**), although it also caused a significant drop in heart rate. (Column 1: Mean value at baseline); Column 2:Values prior to PHE infusion Column 3:Lowest value post-bolus and during infusion; P values are the differences from baseline).

Table 5 Hemodynamic measurements from Alahuhta et al. (1992)

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Source: Table 2, Alahuhta et al., (1992)

Subpopulations

Differences in the responses to PHE subpopulations were reviewed in Section 5.5

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(b) (4)

7.2. Safety

7.2.1. General safety considerations

The number of patients exposed to phenylephrine for the indication of the treatment of hypotension, which totaled 502, is adequate. (b) (4) It is not possible to determine whether any patients participated in more than one of the treatment studies. Some publications did not provide any safety data. However, the number of exposures should be adequate to identify any life-threatening or severe AEs that occur with the treatment administration in adults.

(b) (4)
(b) (4)

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7.2.2. Safety findings from submitted clinical trials

7.2.2.1. Deaths

No deaths were described in the literature that supported the safety database.

7.2.2.2. SAEs

Dr. Jiang noted in his review of the literature that potentially life-threatening adverse events were reported; however, the articles generally did not specify whether these events met the

regulatory criteria for being serious adverse events. These events included hypertension and arrhythmias.

Uncited by the Applicant, literature searches performed by the Clinical team and the consultants from DBRUP both identified two cases of hypertensive emergency:

- [redacted] (b) (4)

- Used to treat hypotension, PHE was reported to associate with a case of hypertensive emergency in a healthy woman undergoing spinal anesthesia for an elective cesarean section at term[25]. However, because she received both PHE and ephedrine, the relative contribution of each vasopressor to her hypertensive episode cannot be ascertained. Her induction of anesthesia was accompanied by an infusion of PHE 100 mcg/min. Within five minutes, she became hypotensive (63/44 mmHg) though her heart rate remained normal (70 beats per minute). Despite being given 9 mg of ephedrine, her blood pressure remained 66/52 mmHg and her heart rate dropped to 30 beats per minute. She was then given another 15 mg of ephedrine and 600 mcg of atropine. She soon complained of chest pain and shortness of breath; with her blood pressure rising to 188/99 mmHg and heart rate 140 beats per minute, PHE infusion was discontinued. A healthy male infant was delivered within 12 minutes of spinal injection. Cardiac work-up and subsequent urgent cardiac catheterization showed that the mother had had a coronary artery dissection.

7.2.2.3.Discontinuations due to AEs

The Applicant did not report on or conduct an analysis of the dropouts and discontinuations. This is expected given the acute use of phenylephrine in the surgical setting and the short duration of follow-up, which was generally limited to the time in the operating room and post-anesthesia care unit following surgery.

7.2.2.4.General AEs,

Dr. Jiang noted that adverse events did not seem to be collected in a consistent manner across studies; some had only AEs in the cardiac or GI systems while others had AEs from all system organ classes. Overall, the adverse events were consistent with what is expected from the exaggerated pharmacodynamic effects of an alpha agonist. These AEs included Nausea, bradycardia, vomiting and hypertension (c.f., Table 19 from the Primary Clinical review).

24 [redacted] (b) (4)
Case report: spontaneous coronary artery dissection during elective caesarean section under spinal anaesthesia. Newell CP et al. Anaesthesia 2011; 66:615-619

(b) (4)

(b) (4)

Dose responsiveness

Dr. Jiang noted the study of Schwinn and Reves (1989) which compared single bolus doses of PHE (50, 100, 150 or 200 mcg) administered during general anesthesia for coronary artery graft surgeries. Decreases in heart rate, though not classified as bradycardia, were seen with the higher two doses.

Other data

Pruritus was reported from a single study (Langesaeter et al., 2008). In this study 9 patients (11.3%) had severe pruritus and 59 patients (73.8%) had little or moderate pruritus. The distribution of pruritus amongst groups receiving PHE (n = 40) and those receiving anesthetic alone (n = 40) was not presented, and the authors did not comment further on this finding.

7.2.2.5. Vitals, EKGs and Lab Assessments

No routine clinical testing was performed by the Applicant or included in the literature. The Applicant neither summarized nor analyzed the limited ECG information provided in literature except the cardiac ischemia (defined as ST-segment depression > 1 mm) by El-Tahan (2011).

(b) (4)

13). PHE patients also required greater rescue nitroglycerine (consistent with the reports of more ischemic episodes).

[26] ST segment depression > 1mm

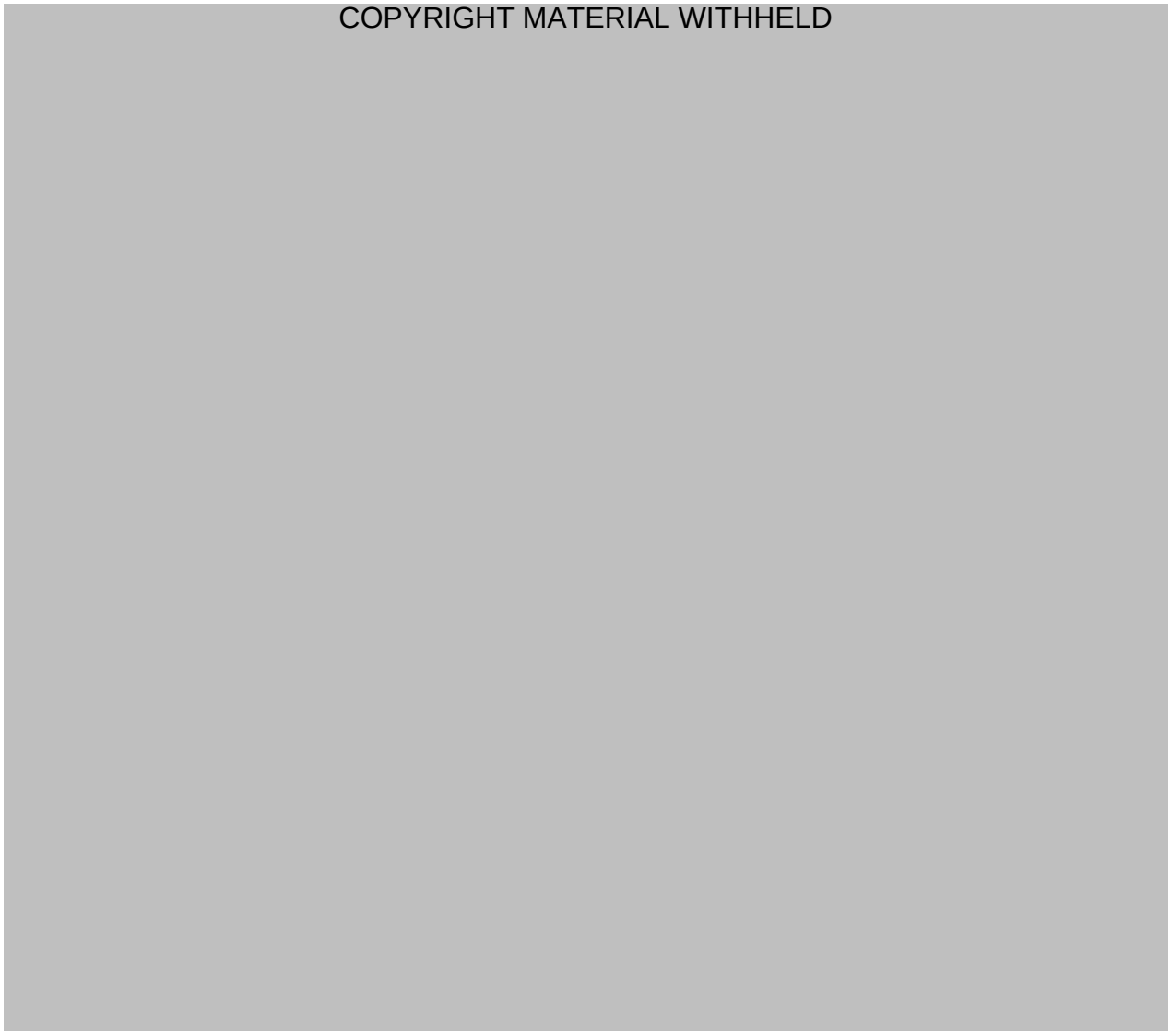
Table 13 Clinical Data from the El-Tahan et al., (2011) Study

Source: El-Tahan et al., Table 2

7.2.2.6. Other tests.

Cardiac Indices

The study of Langstaeder which evaluated PHE for the (b) (4) of hypotension in women after neuraxial anesthesia used continuous invasive recording of arterial BP, cardiac output (CO), and systemic vascular resistance (SVR) in healthy pregnant women receiving (b) (4) PHE or placebo after neuraxial anesthesia. There was a marked reduction in ut and increase in SVR in the PHE arms relative to placebo.



Similar changes in cardiac indices were noted in the paper by El-Tahan.

7.2.1. Safety update

The Applicant provided a safety update that included an article by Mohta et al. (2013) that reported on a potential disease (hypothyroidism) and drug interaction leading to a poor response to PHE.

7.2.2. Immunogenicity, where pertinent

The Applicant provided no information regarding the immunogenicity of PHE. None could be found in the literature. PHE is a simple, low molecular weight phenol derivative and is not expected to be immunogenic.

7.2.3. Special safety concerns

Fetal Safety

Dr. Jiang noted from the Allen (2011) study that with the use of four different PHE infusion rates in low-risk parturients (25, 50, 75, and 100 mcg/min), no differences were observed among the groups with respect to: Apgar scores at 1 and 5 minutes, umbilical cord blood gases, incidence of fetal acidosis (umbilical artery pH < 7.2), and umbilical artery base excess.20 These findings were consistent with those reported by Stewart et al., (2010) who compared PHE infusion rates at 25, 50, and 100 mcg/min.

Using Doppler, Robson et al[27]. showed that maternal cardiac output, specifically the maximum change in CO, correlates more closely with uteroplacental blood flow than upper arm blood pressure measurement. Using Doppler echocardiography to measure changes in cardiac output, Stewart et al. also demonstrated that the reduction in maternal cardiac output was directly attributable to the decrease in heart rate. Cardiac output decreased with time of infusion within each treatment group as well as between groups. The maximum percentage reductions in cardiac output from baseline values were 8%, 15%, and 22% in women receiving 25, 50, and 100 mcg/min, respectively. In order to maintain maternal cardiac output (and oxygen delivery to the fetus), the authors cautioned against using PHE infusion rates sufficient to cause maternal bradycardia and the expected decrease in cardiac output.

7.2.3. Postmarketing Requirements / Commitments/ Agreements

Dr. Jiang noted that the Applicant requested a deferral from pediatric studies (b) (4) based on section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act. The deferral request for age less than 12 years was granted by the Pediatric Research Committee (PeRC) on March 5, 2014, but Sponsor should be required to study pediatric patients 12 to 16 years (inclusive).

7.2.4. Recommendation and Conclusion on Approvability

Dr. Jiang recommended approval of PHE for the treatment indication. I agree with this but suggest adding the phrase ***primarily from vasodilation*** *so the indication would be:*

> *PHE is an alpha-1 adrenergic receptor agonist indicated for increasing blood pressure in adults with clinically important hypotension resulting* ***primarily from vasodilation,*** *in the setting of anesthesia.*

for reasons discussed in my review (see Section **13.1**).

(b) (4)

[27] Robson SC, Boys RJ, Rodeck C, et al. Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective caesarean section, Br J Anaesth 1992;68(1):54-9.

(b) (4)

8. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety of PHE for the treatment (b) (4) of hypertension associated with anesthesia.

9. Other Relevant Regulatory Issues

Office of Surveillance and Epidemiology (OSE) Pharmacovigilance Review
The OSE search of the FAERS database, conducted by Drs. Argual and Gilbert, retrieved 137 reports. There were 12 unique FAERS cases coded with an outcome of death. Analysis of these reports did not find any report of death causally linked to use of IV PHE; nor were there any unique patterns of adverse events across age groups, gender, country of reporter, or location of use. The published literature search of adverse events associated with PHE retrieved one article describing stress cardiomyopathy in an obstetric patient undergoing spinal anesthesia, as well as a number of articles reporting maternal bradycardia (labeled) in obstetric patients. The majority of articles retrieved from a review of the published medical literature focused on the *efficacy* of PHE.

Their review of all unlabeled adverse events did not find any events that were sufficiently compelling to suggest a new safety signal or to require any addition to the proposed PHE labeling. DPV will continue routine monitoring of all adverse events reported in association with PHE HCl 1% injection.

10. Financial Disclosure

Financial Disclosures – Not applicable. No new clinical trial data were reviewed for this application.

11. Labeling

11.1. Proprietary name

The preliminary proprietary name review of September 13, 2013 commented that the proposed proprietary name is acceptable. The review noted that the proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA.

11.2. Physician labeling

From PMHS-PMO

The labeling language proposed by the sponsor for Subsection 8.4 Pediatric Use should be removed and replaced by the following statement: "Safety and effectiveness in pediatric patients have not been established."

The PMHS-MHT was consulted for input from PMHS for appropriately labeling the product, including risk summary for specific populations (maternal, pregnancy category, etc). The PMHS-MHT has provided recommendations for language for the Pregnancy (8.1) and Nursing Mothers (8.3) sections. Information formerly contained in Section 8.2 Labor and Delivery was recommended for Section 8.1 as stipulated in the PLLR.

From DMEPA
DMEPA provided comments for consideration by the review Division primarily regarding the Dosing and Administration section. These suggestions have been incorporated in the Division's consideration of the labeling.

12. DSI Audits

Since the evidence for this application was based on published literature, no site inspections were conducted.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

For the indication of treatment of hypotension during anesthesia:

I recommend approval of PHE for treatment of hypotension during anesthesia. The wording of the indication should be modified to read as follows:

PHE is an alpha-1 adrenergic receptor agonist indicated for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in the setting of anesthesia.

The evidence summarized by the Applicant has adequately demonstrated that administration of PHE has the effect of increasing blood pressure, resulting in the benefit of temporarily relieving hypotension and improving organ perfusion.

The principle risks associated with PHE include hypertension and bradycardia. PHE is also associated with a decrease in cardiac output, increased indices of cardiac work, and increased systemic vascular resistance. This is acceptable if the hypotension is clinically significant depending on the patient condition. The acceptability of these risks is also based on the treatment being a temporizing measure while conditions leading to the hypotension are corrected. Most of the known risks of PHE administered in the setting of anesthesia can be monitored and treated. Furthermore, most adverse effects of PHE administered in the treatment of hypotension occur soon after the administration of PHE in a well monitored setting.

Importantly, the indication of the treatment of clinically important hypotension resulting primarily from vasodilation associated with anesthesia is for a population that may clinically benefit from an elevation of blood pressure. Prolonged decreased blood pressure of hypotension has risks including, stroke, decreased organ perfusion, myocardial ischemia, and death. The risks of PHE treatment are offset by the benefit in preventing these sequelae of hypotension.

While there were no data submitted by the applicant that directly demonstrates a clinical benefit (e.g., mortality or functional outcomes) from the treatment of perioperative hypotension, such data from adequate and well-controlled trials would not likely be obtained since clinically significant outcomes such as mortality or organ failure are uncommon and the conduct of such trials would be considered to be unethical. Observational studies may provide this data; however, modern standard of care mandates treatment of hypotension before significant adverse outcomes. Furthermore, patients experiencing clinically significant outcomes typically have comorbidities that confound interpretation of these studies.

There are perioperative data from observational studies that suggest hypotension is associated with increased morbidity and mortality.

- An intraoperative MAP of less than 55 mm HG results in an increased risk of acute kidney injury (an increase of creatinine by 1.5 fold or 0.3 mg/dl from the preoperative and postoperative periods) and myocardial ischemia with increasing risk as the duration of hypotension increases[28]. Intraoperative hypotension (< 80 mm Hg / min) is also a predictor of increased 1 year mortality (relative risk = 1.036/min; P = 0.0125)[29].

In settings outside of the OR, hypotension has also been correlated with significant morbidity.

- Jones et al., demonstrated odds ratios of 3 and 4.6 for inpatient mortality in two medical centers for patients demonstrating a SBP of less than 100 mm Hg during transport. A SBP < 90 mm Hg predicts an increased risk of in-hospital mortality from cardiac arrest[30]. Hypotension (SBP < 90 mm Hg) is also one of the variables associated with acute large bowel ischemia that required resection or resulted in death[31]. In the POISE trial, a study of the perioperative effects of metoprolol versus placebo, clinically significant hypotension (SBP < 100 mm Hg) was associated with an increased incidence of postoperative stroke (OR 2.14)[32].

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[28] Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Anesthesiology. 2013 Sep;119(3):507-15.

[29] Anesthetic management and one-year mortality after noncardiac surgery. Monk TG, Saini V, Weldon BC, Sigl JC. Anesth Analg. 2005 Jan;100(1):4-10.

[30] Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Resuscitation. 2004 Aug;62(2):137-41.

[31] Epidemiology, clinical features, high-risk factors, and outcome of acute large bowel ischemia. Longstreth GF, Yao JF. Clin Gastroenterol Hepatol. 2009 Oct;7(10):1075-80.

[32] Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC,

These data suggest that hypotension results in serious sequelae. Treatment with an appropriate therapeutic in conjunction with evaluating and addressing the etiology may be required to minimize the potential injury or death.

Two further considerations were taken into account in my consideration of the risk benefit analysis for the approval and labeling of phenylephrine.

- Hypotension can be caused by a number of (or combination of) etiologies, such as vasodilation, hypovolemia, or low cardiac output. The alpha effect of phenylephrine would likely worsen the clinical effects of hypotension of the latter 2 causes, so the indication should be for hypotension resulting primarily from vasodilation, associated with anesthesia. Perioperative hypotension associated with neuraxial anesthesia and general anesthetic agents is believed to originate from vasodilation, particularly from their sympatholytic effects. Treatment of hypotension not responsive to phenylephrine therapy should prompt investigations into and, if appropriate, treatment of other etiologies.
- While phenylephrine has been used in the perioperative setting for an extensive period, direct evidence of clinical benefit has not been evaluated. The cause of the vasodilation resulting in hypotension should be addressed and phenylephrine should be used to temporarily increase blood pressure if appropriate.

Based on my overall consideration of benefits and risks for this proposed indication, the benefits of PHE outweigh the risks to treat the clinically important hypotension during anesthesia.

(b) (4)

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13.2. Safety concerns to be followed postmarketing
13.2.1. Risk Minimization Action Plan, if any

I do not feel a plan beyond routine post-marketing pharmacovigilance is required for this approval given its known safety profile, long history of use, and well established practices of perioperative monitoring of blood pressure.

13.3. Postmarketing studies, voluntary or required
13.3.1. CMC

PMC 1
Éclat commits to establish final, data-based (b) (4) acceptance criteria for the content of sodium metabisulfite in the drug product, (b) (4) (b) (4)

PMC 2
Éclat commits to (b) (4) release acceptance criteria (b) (4) for the content of sodium metabisulfite in the drug product, (b) (4) (b) (4) .

AGREEMENT 1
Éclat agrees to provide annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches, as described in NDA amendment dated March 11, 2014. The analysis will be focused on different instability trends for smaller fill volumes with a large head space (i.e., 1 mL and 5 mL) in comparison to the 10 mL fill volume with a small head space. Also, Éclat agrees to submit an evaluation of trends in sodium metabisulfite content in the context of changes in pH and impurity levels as well as analyze the impact of storage orientation on instability trends. The first report is scheduled to be submitted by April 2015, and it will contain analysis of 6 months stability data collected at the accelerated (40 ± 2 °C/75% ± 5% RH) and at long-term (25 ± 2°C/60% ± 5% RH) storage conditions for commercial manufacturing.

13.3.2. Pharm / Tox

PMR 1
Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

PMR 2
Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

PMR 3
Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

PMR 4
Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

A teleconference will be conducted after the submission of this memo between the Division and the Applicant to discuss the PMRs and their associated timelines.

13.3.3. PREA

The Division met with the PERC on and there was agreement that study of the 12 to 17 year (b) (4). The Division recommended to the PERC that studies in this age group will include pharmacokinetics, efficacy and safety.

We agreed on the following PREA requirement:

Clinical Studies: : Conduct a study in the ≥12 - 16 year old age group to evaluate the dose effect of PHE injection on blood pressure in patients undergoing general anesthesia and neuroaxial anesthesia. Administration by both the bolus and infusion methods must be studied for the treatment of hypotension. Dosing of PHE should be weight-based since weight may be quite variable in this population. Dosing should be based on the patient's hemodynamic status.

Evaluation of different dose levels (e.g., mg/kg, in the case of boluses and mcg/kg/min, in the case of infusions) will be needed to assess the dose: effect relationship.

The information you capture needs to include, at a minimum, the following:

- Demographics: Demographic and medical history information that informs about the subjects' cardiovascular status.
- Efficacy/Pharmacodynamics: Blood pressures and heart rate, time to onset and maximal response and duration of response should be defined and captured before and during the treatment.
  - Concomitant intraoperative and post-operative medications, including their doses and adjustments in inhaled gas concentration or intravenous agent infusion rates.
  - Interventions used to treat the hypotension, e.g., other pressor agents, intravenous fluid boluses, changes in patient positioning.
  - Intraoperative events relevant to subjects' physiological status, such as blood loss and fluids administered.
- Pharmacokinetics: Need to be characterized at points relative to the PHE administration.
- Safety: Vital signs (consistent with American Society of Anesthesiology Monitoring Guidelines), Adverse Events, and Electrocardiograms (EKG) should be collected. Where possible continuous monitoring should be used (e.g., Pulse oximetry, temperature, and EKGs)

Required subjects:
25 subjects in bolus treatment group / dose level
25 subjects in infusion treatment group / dose level

A timeline for the required studies must be submitted including the following dates:
Final Protocol Submission: April 28, 2015
Trial Completion: April 28, 2018
Final Report Submission: November 1, 2018

13.4. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

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/s/

CHRISTOPHER D BREDER
04/07/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204300
Priority or Standard	Standard
Submit Date(s)	June 28, 2013
Received Date(s)	June 28, 2013
PDUFA Goal Date	June 27, 2014
Division / Office	DAAAP/ODE2
Reviewer Name(s)	Timothy T. Jiang, MD, PhD
Review Completion Date	March 20, 2013
Established Name	Phenylephrine Hydrochloride Injection, USP, 1%
(Proposed) Trade Name	
Therapeutic Class	Vasoconstrictor, vasopressor
Applicant	E'clat Pharmaceuticals
Formulation(s)	Injection
Dosing Regimen	Intravenous bolus and infusion
Indication(s)	Treatment (b) (4) of hypotension during anesthesia
Intended Population(s)	Adults

Clinical Review
Timothy Jiang, MD, PhD
Phenylephrine Hydrochloride
NDA204300

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

For the indication of treatment of hypotension during anesthesia:

I recommend approval for phenylephrine (PHE) for treatment of hypotension during anesthesia. The wording of the indication should be modified to read as follows:

> *Phenylephrine Hydrochloride is an alpha-1 adrenergic receptor agonist indicated for increasing blood pressure in adults with clinically important hypotension in the setting of anesthesia.*

(b) (4)

1.2 Risk Benefit Assessment

For the indication of treatment of hypotension during anesthesia:

The benefits of phenylephrine to treat hypotension are predicated on its ability to temporarily revers hypotension, and potentially improve organ perfusion during anesthesia.

The most common risks associated with phenylephrine administered as a treatment for hypotension include hypertension and bradycardia, which are related to the drug's mechanism of action.

Phenylephrine is also associated with a decrease in cardiac output, increased indices of cardiac work, and increased systemic vascular resistance. This is acceptable for the treatment of hypotension in order to reverse hypotension and maintain systemic perfusion pressure if the hypotension is clinically significant (i.e., > 20% of baseline). The acceptability of these risks is also based on the treatment being a temporizing measure while conditions leading to the hypotension are corrected.

Most of the known risks of phenylephrine administered in the setting of anesthesia can be monitored and treated. Most adverse effects of phenylephrine administered in the treatment of hypotension occur soon after the administration of phenylephrine in a well monitored setting.

Based on my overall consideration of benefits and risks for this proposed indication, the benefits of phenylephrine outweigh the risks to treat the clinically important hypotension during anesthesia.

(b) (4)

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(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Standard pharmacovigilance approaches will be applied to postmarketing risk management of phenylephrine.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant requested a deferral from pediatric studies (b) (4) based on section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act.

The deferral request for age less than 12 years was granted by the Pediatric Research Committee (PeRC) on March 5, 2014, but Sponsor should be required to study pediatric patients 12 to 16 years.

2 Introduction and Regulatory Background

2.1 Product Information

Phenylephrine is a synthetic sympathomimetic agent and selective alpha 1 direct-acting adrenergic receptor agonist. It has been used as a vasopressor, mydriatic and decongestant for decades.

The IV formulation had been a marketed unapproved drug.

Phenylephrine hydrochloride (NDA 203826, West-Ward) was approved in December 2012 for "increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia."

2.2 Currently Available Treatments for Proposed Indications

Phenylephrine (NDA 203826) by West-Ward was approved in December 2012 for *"clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia"*.

Other products available to be used as pressors in perioperative setting include norepinephrine (Levophed), epinephrine, angiotensin, and dopamine. It must be noted that ephedrine is a commonly used but an unapproved product. Because of the relative adrenergic receptor affinities and ability to safely administer peripherally versus centrally, each of these agents has a different utility in the treatment of hypotension.

2.3 Availability of Proposed Active Ingredient in the United States

Phenylephrine (NDA 203826) by West-Ward is approved for *"clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia"*.

Phenylephrine is available as an OTC nasal decongestant. Phenylephrine is also used in ophthalmic preparation to induce mydriasis.

2.4 Important Safety Issues With Consideration to Related Drugs

The product label contains the following warnings and precausions:

If used in conjunction with oxytocic drugs, the pressor effect of sympathomimetic pressor amines is potentiated.

This product contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

<u>From IND to Pre-NDA</u>
Phenylephrine was developed under IND 113044 with the following time lines:

- IND submission August 3 2011
- Type B Meeting November 17, 2011
- EOP2 Meeting September 27, 2012
- Pre-NDA Meeting December 6, 2012

Type B meeting Key Comments:

- Data from the various clinical studies should be evaluated individually and should be integrated to allow a meaningful benefit-risk analysis.
- The studies provided do not appear to be adequate to provide the needed information:
  - the literature studies are so varied in the doses administered, routes of administration (intravenous, intramuscular and epidural) and methods of

administration (bolus and infusions) for induction of general anesthesia and spinal anesthesia
  - there is not enough information to identify a dosing regimen suitable for labeling
- "Your submission is not adequate to support filing an NDA, and you will need to identify an appropriate dosing regimen to guide in the gathering of suitable data to allow a benefit risk analysis when the NDA is submitted."

End-of-Phase 2 meeting Key Comments

(b) (4)

- Safety database of at least 300 subjects
- Provided instruction how to organize the NDA

Pre-NDA Key Comments

- West-Ward's indication subsumes your indication for the treatment of hypotension during anesthesia.
- Proposed to not rely on the finding of safety and effectiveness for this approved product by West-Ward.
- "If you intend to rely on the Agency's finding of safety and effectiveness for West-Ward's approved phenylephrine hydrochloride drug product for the treatment indication, (b) (4), any reliance on the former would not itself bar the filing or review of a 505(b)(2) NDA for both the (b) (4) and treatment indications."

Refuse to file (RTF)
Original NDA was submitted on February 7, 2012.
RTF letter was issued on April 5, 2013, and the Division met the Sponsor with Type A meeting on June 13, 2013.

Filing deficiencies (RTF):

- Did not provide an adequately constructed Integrated Summary of Efficacy (ISE)
- Did not provide an adequately constructed Integrated Summary of Safety (ISS)
- Did not separate your discussions of the two proposed indications in your ISS and ISE

During Type A meeting, the Divisor elaborated above deficiencies. The Sponsor re-submitted the NDA before the Division issued the meeting minutes.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The information contained in the resubmission was adequate to allow a comprehensive review of safety and efficacy.

3.2 Compliance with Good Clinical Practices

The Applicant neither conducted clinical studies nor obtained original protocols for the studies reported in the literature that provided the clinical evidence of safety and efficacy for this NDA. Therefore, it is not possible to determine the extent to which the data were derived from studies conducted in compliance with Good Clinical Practices regulations.

3.3 Financial Disclosures

No clinical studies were conducted by the Applicant in support of this NAD. Therefore, financial disclosures were neither required nor submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drs. Eugenia Nashed and Julia Pinto reviewed this application. The final review is pending, and this reviewer is not aware of any outstanding issues that would preclude approval providing post-marketing commitment is required as follows:

Content of sodium metabisulfite:
Content will be monitored on stability and final acceptance criteria (b) (4)

Leachables:
Since the data documenting presence or absence of leachables from [(b) (4)] taking into account the drug substance structure characteristics (i.e., [(b) (4)]) and the presence of [(b) (4)] are not submitted, include, as a preventive safety measure, the method and acceptance criteria for the content of potential [(b) (4)] extractable to the stability protocol (consult with [(b) (4)] Team).

4.2 Clinical Microbiology

Dr. Stephen Langille reviewed this application, and recommended approval.

4.3 Preclinical Pharmacology/Toxicology

Drs. Marcus Delatte and Daniel Mellon reviewed the application, and recommended approval. Drs. Marcus Delatte and Daniel Mellon provided the following additional non clinical recommendations:

Based on the data submitted to date, the following studies are recommended as postmarketing requirements (PMRs), should this NDA be approved during this cycle:
1. Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

2. Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

3. Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

4. Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

4.4 Clinical Pharmacology

Drs. David Lee and Yun Xu reviewed this application, and recommended approval.

4.4.1 Mechanism of Action

Phenylephrine is a selective alpha1-adrenergic receptor agonist.

4.4.2 Pharmacodynamics

According to Drs. Lee and Xu, “Phenylephrine’s vasopressor effect (measured by mean arterial pressure) is reported to be typically 30 to 150 seconds in duration after a bolus administration (Goertz et al. 1993a, Dyer et al. 2009).” Single bolus at dosing range of 50 to 150 mcg increases MAP by about 20 mm Hg.

4.4.3 Pharmacokinetics

Drs. David Lee and Yun Xu provided the comments as follows:

Following an intravenous infusion (12.5 to 20 minutes) of 1 mg (mean dose of 0.84 ± 0.17 mg) tritiated phenylephrine (3H-PE), the PE concentration-time curve exhibited biphasic decline, as observed by an initial rapid distribution followed by relatively slow elimination. The reported average steady state volume of distribution (Vss) and elimination half-life were 340 L (range 184 to 543 L) and 151 minutes (2.51 h based on β-phase), respectively. The observed distribution phase was rapid (less than 5 minutes based on α-phase).

Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. Based on 3H-PE intravenous administration, approximately 86% (approximately 80% of the administered dose was eliminated within first 12 h) of the intravenously administered dose was recovered in the urine within 48 h. The excreted unchanged drug (i.e., parent PE) was 16% of the dose in the urine at 48 h post intravenous administration. There are two major metabolites with approximately 57 and 8% of the administered dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active.

5 Sources of Clinical Data

No new clinical efficacy studies were performed in support of this application. The source of clinical data was the published literature provided by the Applicant.

In order to support the efficacy for the indication of the treatment of hypotension during anesthesia, the Applicant identified 16 publications. As a 505(b)(2) application, the Applicant did not rely on the Agency’s previous findings of efficacy and safety for the approved drug phenylephrine hydrochloride (NDA 203826) by West-Ward Pharmaceuticals, but rely on published literature only

This review not in any way or shape relies on the Agency’s previous findings of efficacy and safety for the approved drug phenylephrine hydrochloride (NDA 203826) by West-Ward Pharmaceuticals (NDA203826), but relies solely on published literature.

(b) (4)

5.1 Listing of Studies/Clinical Trials

In order to support efficacy of treatment, the Applicant identified 16 as the table below:

Table 1 Clinical Studies from Literature Submitted to Support the Indication of Treatment of Hypotension

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
General Anesthesia							
Goertz et al. 1993a Germany	Randomized cross-over study of PE vs. norepinephrine in isoflurane-induced hypotension (n=16) Elective minor abdominal or orthopedic surgery General anesthesia with thiopental Study conducted after induction of anesthesia but prior to surgical procedure	Efficacy, Safety	16 patients (7M/9F) with no known cardiovascu-lar disease 36 years (31-41) 74 kg (66-82) ASA status I, II Race not specified	PE: When MAP ≤ 80% of baseline, 2 µg/kg IV bolus PE was administered. Comparator: Norepinephrine (NE) (0.1 µg/kg), administered in same manner. Patients received both PE and NE in random order; after receiving an initial bolus of one drug, patients received a bolus of the other drug after BP and HR returned to baseline levels.	**MAP (mm Hg) (95%CI)** 0 seconds 30 seconds 60 seconds 120 seconds 180 seconds	 61 (56-66) 83 (78-88) 75 (70-81) 72 (68-76) 66 (61-71) Maximal MAP increase of 22 mm Hg seen at 30 sec post-dose.	PE was an effective vasopressor.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
General Anesthesia (Continued)							
Goertz et al. 1993b Germany	Randomized comparison of PE and norepinephrine (NE) Elective coronary artery bypass grafting (n=20) or elective aortic valve replacement (n=18) General anesthesia	Efficacy, Safety	24 patients Coronary artery disease (CAD) group 12M/2F Median 61 years (49-69) Median 75 kg (63-84) Valvular aortic stenosis (AS) group 5M/5F Median 62 years (52-78) Median 69 kg (52-78) ASA status and race not specified	PE: When MAP was >10% less than lowest reading in previous 24 hours, 1 µg/kg bolus of PE was administered via central venous catheter. Comparator: Bolus injection of norepinephrine (0.05 µg/kg), administered in same manner. Patients received both PE and NE in random order; after receiving an initial bolus of one drug, patients received a bolus of the other drug after arterial BP and HR returned to baseline levels.	**MAP over time (CAD group) (mm Hg)** 0 seconds 30 seconds 60 seconds 120 seconds 180 seconds **MAP over time (AS group) (mm Hg)** 0 seconds 30 seconds 60 seconds 120 seconds 180 seconds	 71 (65-76) 93 (86-101) 94 (88-100) 87 (78-97) 80 (75-85) 69 (60-79) 98 (86-111) 99(85-114) 96 (83-109) 82 (69-94)	PE bolus administration is an effective vasopressor in CAD and AS patients.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
General Anesthesia (Continued)							
Schwinn and Reves 1989 United States	Randomized, dose escalation study of effect of PE on cardiovascular endpoints (n=18) Elective coronary artery bypass graft surgery General anesthesia	Efficacy, Safety	18 patients 14 had hypertension; 5 had diabetes; 11 had a myocardial infarction; mean ejection fraction = 50.8 ± 8.3 Mean 63.2 ± 5.6 years Gender, weight, ASA status, and race not specified	PE: 50, 100, 150 and 200 µg IV bolus doses of PE Doses were administered in random sequence to the same patients during anesthesia. The 150 and 200 µg doses were added later in the study. Comparator: None	**MAP** **SVR**	Intravenous bolus PE was associated with significant increases in MAP above baseline levels in all patients. Peak hemodynamic effects occurred 42 seconds after administration. Effects of PE doses >100 µg were generally greater than with the lowest 50 µg dose. A dose-dependent trend increase in SVR was observed. Mean time to peak SVR was 41.2 ± 1.4 seconds after PE injection in all patients.	Bolus administration of PE is effective in increasing blood pressure, SVR and decreasing cardiac output and heart rate in patients with myocardial disease.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia							
das Neves et al. 2010 Brazil (also included in Tables 19, 24, 39, and 40 for the prevention indication)	Prospective, randomized double-blind study of prophylactic infusion of PE (Group 1; n=40), prophylactic bolus of PE (Group 2; n=40, or bolus of PE to treat hypotension (Group 3; n=40) Elective Cesarean delivery Spinal anesthesia	Efficacy, Safety	120 F (40/group) Group 1 Mean 30.78 ± 5.93 years Mean 74.03 ± 8.34 kg Group 2 Mean 29.8 ± 6.06 years Mean 74.63 ± 9.22 kg Group 3 Mean 29.3 ± 5.45 years Mean 76.45 ± 9.52 kg ASA status I Race not specified	PE: Group 1: Continuous IV infusion of 0.15 µg/kg/min, administered after spinal block. Group 2: Prophylactic IV bolus of 50 µg, administered after spinal block. Group 3: Intervention IV bolus of 50 µg, administered in case of fall in SBP and/or DBP of up to 20% of mean baseline levels. In all groups, a drop in BP >20% was treated with a bolus of 30 µg PE IV repeated every 2 min. Comparator: None	**Hypotension** Prophylactic infusion Prophylactic bolus Bolus intervention	 17.5% 32.5% 85%	Prophylactic PE was more effective than bolus interventional dosing at managing hypotension, nausea and vomiting and limiting the number of rescue pressor interventions during spinal anesthesia. Prophylactic infusions appeared to be more effective at preventing hypotension, nausea/vomiting and the use of rescue pressors as compared to a single bolus prophylactic dose.
					Nausea Prophylactic infusion Prophylactic bolus Bolus intervention	 10% 15% 40%	
					Vomiting Prophylactic infusion Prophylactic bolus Bolus intervention	 0% 7.5% 12.5%	
					Rescue dose Prophylactic infusion Prophylactic bolus Bolus intervention	 12.5% 30% 70%	

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia (Continued)							
Dyer et al. 2008 South Africa	Prospective observational study of patients (n=15) with severe eclampsia (SBP >160 mm Hg and/or DBP>110 mm Hg or symptoms of severe pre-eclampsia) Urgent but not emergency Cesarean delivery Spinal anesthesia	Efficacy, Safety	10 F 24-40 years; 60-102 kg 3 patients received only PE in the study; the other 7 received ephedrine in addition to PE (as rescue medicine) ASA status and race not specified	PE: If MAP decreased by 20% from baseline, 50 µg PE was administered every minute until BP recovered to within 20% of baseline (if MAP decreased by 30% from baseline, 100 µg PE was administered in same manner). After delivery, PE (50-100 µg) or ephedrine (5-10 mg) was administered to maintain MAP within 30% of baseline pressure. Comparator: None	**MAP (mm Hg) (SD)** Pre-delivery Post-delivery Mean increase in MAP	 91 ± 13 108 ± 15 17	PE bolus doses of 50 µg and 100 µg were effective in increasing MAP when used as the first choice vasopressor. The time to peak response to PE vasopressor effects was the same for first and subsequent doses, with peak responsiveness seen between 24 and 40 seconds post-dose.
					Dose before delivery and no. of patients 0 µg 50 µg 100 µg	 n=7 n=7 n=1	
					Dose after delivery and no. of patients 0 µg 50 µg 100 µg 150 µg	 n=9 n=3 n=1 n=2	
					Time to peak effect (vasopressor) (sec) First dose Second dose Third dose	 28.3 (4.2) 39.6 (30.0) 24.6 (3.2)	

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia (Continued)							
Dyer et al. 2009 South Africa	Prospective, randomized, double-blind comparison of bolus PE (n=20) and ephedrine (n=20) Elective Cesarean delivery Spinal anesthesia Sub-study of 20 patients received 2.5 IU oxytocin administered after delivery either with (n=10) or without (n=10) PE	Efficacy, Safety	20 healthy F 12 received PE pre-delivery, 8 received PE post-delivery, 10 received PE in combination with oxytocin Mean 27.1 ± 3.7 years Mean 73.7 ± 3.7 kg ASA status and race not specified	PE: If MAP decreased by 20% from baseline, 80 µg was administered every 60 s until MAP recovered to within 20% of baseline. If MAP continued to decrease to 40% below baseline, a rescue dose was given. Comparator: Ephedrine (10 mg) administered in same manner.	**MAP**	PE caused a higher increase in MAP than that seen with ephedrine (increase ~15.7 mm Hg seen at 61.8 seconds compared to ~7 mm Hg increase seen at 89.8 seconds post-dose). When PE was given in combination with oxytocin, MAP was increased ~40% from baseline, while MAP in oxytocin only group was decreased 50% from baseline.	PE was better at reversing hypotension than ephedrine. When given concurrently with oxytocin, PE effectively abrogated oxytocin induced hypotension, and possibly caused transient hypertension.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia (Continued)							
Kee et al. 2007 China	Randomized, double-blind comparison of PE (n=74) and ephedrine (n=74) Emergency Cesarean delivery Spinal anesthesia	Efficacy, Safety	74 F Age, weight, ASA status, and race not specified	PE: Each time SBP (measured every minute) decreased to <100 mm Hg, a 100 µg IV bolus of PE was given. Comparator: Ephedrine (10 mg bolus) administered in same manner.	**Nausea/vomiting** as indirect measure of PE effectiveness	PE group had 4% incidence of nausea/vomiting compared to 30% seen in the ephedrine group, despite similar minimum recorded blood pressure.	PE can be used safely and effectively in emergency Cesarean delivery.
Moran et al. 1991 United States	Randomized, double-blind comparison of PE (n=31) and ephedrine (n=29) Elective Cesarean delivery Spinal anesthesia	Efficacy, Safety	31 healthy F Age, weight, ASA status, and race not specified	PE: Initial IV bolus of 80 µg PE for a decrease of >5 mm Hg or greater from baseline SBP, followed by additional boluses of 40-80 µg to maintain SBP above 100 mm Hg throughout surgery.	**MAP** **Nausea/vomiting**	Reported in text to be effective for blood pressure management. 25 incidents of nausea and vomiting were observed in this study, although it is not clear if this were related to hypotension.	PE was stated to be effective in treating hypotension, but data were not provided. PE had similar frequency of nausea/vomiting compared to ephedrine group.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results			Efficacy Conclusion
Neuraxial Anesthesia (Continued)									
George et al. 2010 Canada	Double-blind, up-down study to identify ED_{90} of PE (n=66) Elective Cesarean delivery Spinal anesthesia	Efficacy, Safety	45 healthy nonlaboring F Mean 34 ± 5 years Mean 86 ± 15 kg ASA status I, II Race not specified	PE: If SBP decreased >20% of baseline or to an SBP <90 mm Hg, an initial bolus of 100 µg IV PE was given; subsequent doses (in increments of 20 µg) were based on the response of the preceding subject per a biased-coin design up-down sequential method Comparator: None	**Successful response to treatment** (return to within 20% of baseline systolic pressure, or SPB ≥90 mm Hg within 1 min) **Dose (µg)** 80 100 120 140 160 180	**Succes-ses** 1 13 10 4 6 2	**Trials** 3 17 11 5 7 2	**Success rate** 0.33 0.76 0.91 0.80 0.86 1.00	PE effectively managed hypotension. The only dose with 100% success rate was 180 µg. ED_{90} estimated to be 147 µg (95% CI, 98-222 µg).

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia (Continued)							
Moran et al. 1991 (Cont'd.) United States				Comparator: Ephedrine; initial IV bolus of 10 mg, followed by additional boluses of 5 mg/mL, administered as above.			
Prakash et al. 2010 India	Randomized, double-blind comparison of PE (n=30) and ephedrine (n=30) Elective Cesarean delivery Spinal anesthesia	Efficacy, Safety	30 F Mean 24.1 ± 4.4 years Mean 58.7 ± 5.6 kg ASA status I Race not specified	PE: Whenever SBP decreased to 80% of baseline, a 100 µg bolus was administered. Additional boluses given if SBP remained at or below ≤ 80% of baseline. Comparator: Ephedrine (6 mg bolus), administered in same manner.	**No. of vasopressor doses**	2 (1-3)	Intravenous bolus doses of PE are effective in the treatment of hypotension following spinal anesthesia in patients undergoing Cesarean delivery. PE 100 µg has similar efficacy to ephedrine 6 mg.
					Total vasopressor dose (µg)	160 ± 60	
					Minimum SBP (mm Hg)	93 (70-110)	
					Maximum SBP (mm Hg)	127 (100-150)	
					Nausea and dizziness	No women receiving PE complained of nausea or dizziness.	

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
Neuraxial Anesthesia (Continued)							
Thomas et al. 1996 United Kingdom	Randomized parallel comparison of PE (n=19) and ephedrine (n=19) Elective Cesarean delivery Spinal anesthesia	Efficacy, Safety	19 healthy F Mean 30.0 years (95% CI:27.9-32.1) Mean 71.0 kg (66.8-75.2) ASA status and race not specified	PE: Whenever SAP decreased to ≤ 90% of baseline, 100 µg bolus of PE was administered. Arterial pressure was measured at 1 minute intervals. Comparator: Bolus injections of ephedrine (5 mg) administered in same manner.	**Mean number of PE boluses used**	6 bolus injections (1-10 range)	Maternal arterial pressure was effectively restored with PE administration.
					SAP	Baseline SAP dropped 23.1% after induction of spinal anesthesia. Administration of PE returned SAP to almost baseline levels.	
Combined General and Neuraxial Anesthesia							
Ishiyama et al. 2003 Japan	Randomized, parallel comparison of PE (n=17) vs. ephedrine (n=17) vs. none (n=9) Elective surgery Combined general (propofol) and epidural (ropivacaine) anesthesia	Efficacy, Safety	17 patients (7M/10F) Mean 63 ± 14 years Mean 56 ± 13 kg ASA status I, II Race not specified	PE: If mean BP decreased >30% of preanesthetic valued, 2 µg/kg IV PE was administered. Comparator: Ephedrine (0.1 mg/kg IV) administered in same manner.	**MAP**	Mean MAP response approximately 19 mm Hg with mean bolus dose of 112 µg PE (estimated from graphical data).	PE increased blood pressure during combined general and epidural anesthesia.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
General Anesthesia							
Kwak et al. 2002 South Korea	Randomized, blind comparison of PE (n=14) and norepinephrine (n=10) Valvular heart surgery or repair of congenital heart defects General anesthesia	Efficacy, Safety	14 patients (3M/11F) with chronic pulmonary hypertension Mean 46.8 ± 12.1 years Weight, ASA status, and race not specified	PE: If SAP decreased to <100 mm Hg, 40 µg/mL was infused (at 50 mL/hr) to raise SBP by 30% and 50% above baseline. Comparator: Norepinephrine (8 µg/mL infused at 50 mL/hr) was administered in same manner.	**SAP** maintained to 30% and 50% above baseline	PE was ineffective in raising SAP in 2 patients after 3 min infusion; these patients were excluded from analysis. SAP was increased to >30% baseline in all other patients treated with PE. However, 6 patients failed to increase to >50% of baseline from T2 to 3 minutes.	Patients with hypertension may have some reduced responsiveness to PE pressor effects during anesthesia.
Nygren et al. 2006 Sweden	Randomized, prospective, interventional cross-over study of PE and norepinephrine (n=10) After completion of uncomplicated coronary artery bypass surgery,	Efficacy, Safety	10 patients (9M/1F) with coronary artery disease and left ventricular fraction >50% Mean 66 years (52-77)	PE: Infusion rate of PE titrated to produce target MAP of 90 mm Hg (0.5 ± 0.22 µg/kg/min). Comparator: Norepinephrine (NE) infusion rate titrated to produce target MAP of 90 mm Hg (0.52 ± 0.009 µg/kg/min).	**MAP**	With propofol dose titrated to produce MAP 65-75 mm Hg, PE infusion 0.5 µg/kg/min (range 0.21-0.94 µg/kg/min) achieved MAP 92 ± 4 mm Hg.	PE infusion was effective at counteracting propofol induced hypotension.

Citation, Country	Study Design, Procedure, Type of Anesthesia	Type of Study	PE-Treated Subjects	PE Dose, Administration, Comparator	Measure of Efficacy	Results	Efficacy Conclusion
General Anesthesia (Continued)							
Nygren et al. 2006 (Cont'd.) Sweden	patients received propofol sedation and mechanical ventilation (propofol dose titrated to establish stable MAP of 65-75 mm Hg)		Weight, ASA status, and race not specified	Patients received both PE and NE randomly and sequentially; MAP was not to exceed 150 mm Hg.	**SVRI**	PE infusion of 0.50 ± 0.22 µg/kg/min (range 0.21-0.94 µg/kg/min) increased SVRI by 46%.	

Source: Applicant's submission ISE (pp. 44-56)

(b) (4)

[redacted]

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5.2 Review Strategy

I am the only primary clinical reviewer on this NDA.

The Applicant is relying solely on published literature for the evidence of efficacy and safety for both the indication of treatment (b) (4) of hypotension during anesthesia despite there being an approved indication for treatment of hypotension during anesthesia for West-Ward Pharmaceuticals phenylephrine hydrochloride injection product (NDA203826).

As commented before, this review not in any way or shape relies on the Agency's previous findings of efficacy and safety for the approved drug phenylephrine hydrochloride (NDA 203826) by West-Ward Pharmaceuticals (NDA203826), but relies solely on published literature.

The efficacy review will mainly be focused on randomized, double-blind studies. (b) (4)

For safety review, the data from the literature and the FDA's Adverse Event Reporting System (FAERS) will be reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Treatment:
The Applicant submitted 16 publications to support the indication of treatment of hypotension during anesthesia.

There are no placebo controlled trials. Most studies are the active-controlled with ephedrine as active comparator.

(b) (4)

The studies reported in the literature used to determine the safety and efficacy of phenylephrine for both indications are summarized in the sections 6, and 7.

6 Review of Efficacy

Efficacy Summary

For the indication of treatment of hypotension during anesthesia:

The Applicant submitted 16 publications to support a finding of efficacy for treatment of hypotension during anesthesia. No placebo controlled studies were identified. Most studies are active-controlled with ephedrine as the active comparator. It is noted that ephedrine is an unapproved product for perioperative hypotension. None of the active controlled studies are designed to show non-inferiority from statistical perspective.

From the ISE, the suggested primary endpoint by the Applicant is *"…to reverse clinically relevant hypotensive effects of anesthesia, in many instances defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline."*

For treatment of hypotension during anesthesia, the published 16 trials demonstrated that phenylephrine reverses hypotension associated with anesthesia. Studies demonstrated that bolus at a range of 50 to 200 mcg increases MAP about 20 mm Hg in 30 to 150 seconds.

Efficacy conclusion for the indication of treatment of hypotension during anesthesia:

Phenylephrine reverses hypotension during anesthesia.

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(b) (4)

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6.1 Indication

The Applicant's proposed language for the product label related to indication is as follows:

> PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, (b) (4) is an alpha-1 adrenergic receptor agonist intended for the treatment (b) (4) of hypotension during anesthesia.

Reviewer's comments:

The Applicant is seeking two separate indications, the treatment (b) (4) of hypotension during anesthesia. (b) (4)

6.1.1 Methods

6.1.1.1 Treatment

The Applicant conducted a review of literature using PubMed. Sixteen published studies were identified to support the use of phenylephrine to treat anesthesia-induced hypotension. None of the papers are placebo-controlled. Active-controlled studies will be used as higher level of evidence than the unblinded studies.

The Applicant tried to retrieve original protocols and data from the authors of the published trials, but they were not able to get any of the source information.

Reviewer's Comments:
The approach taken by the Applicant is acceptable.

6.1.1.2 (b) (4)

(b) (4)

6.1.2 Demographics

6.1.2.1 Treatment

The Applicant provided the following table with demographic information of individual studies but did not integrate these data as the efficacy, and demographic information for individual subjects were not available:

Table 3 Demographics for the Indication of the Treatment of Hypotension

Citation	Gender (M/F)	Age (yrs)	Race/Ethnicity	ASA Status	Geographic Location
Alahuhta et al. 1992	0/8	Mean 28.5 ± 3.3	Not indicated	Not indicated	Finland
Brooker et al. 1997	10/3	Median 62.5 (25-71)	Not indicated	ASA I-II	United States
das Neves et al. 2010	Gp 1: 0/40 Gp 2: 0/40 Gp 3: 0/40	Mean ages: 30.78 ± 5.93 29.8 ± 6.06 29.3 ± 5.45	Not indicated	ASA I	Brazil
Dyer et al. 2008	0/10	24-40	Not indicated	Not indicated	South Africa
Dyer et al. 2009	0/20	Mean 27.1 ± 3.7	Not indicated	Not indicated	South Africa
George et al. 2010	0/45	Mean 34 ± 5	Not indicated	ASA I-II	Canada
Goertz et al. 1993a	7/9	36 (31-41)	Not indicated	ASA I-II	Germany
Goertz et al. 1993b	17/7	49-78	Not indicated	Not indicated	Germany
Ishiyama et al. 2003	7/10	Mean 63 ± 14	Not indicated	ASA I-II	Japan
Kee et al. 2007	0/74	Not indicated	Not indicated	Not indicated	China
Kwak et al. 2002	3/11	Mean 46.8 ± 12.1	Not indicated	Not indicated	South Korea
Moran et al. 1991	0/31	Not indicated	Not indicated	Not indicated	United States
Nygren et al. 2006	9/1	Mean 66 (52-77)	Not indicated	Not indicated	Sweden
Prakash et al. 2010	0/30	Mean 24.1 ± 4.4	Not indicated	ASA I	India
Schwinn and Reves 1989	18 – Gender not specified	Mean 63.2 ± 5.6	Not indicated	Not indicated	United States
Thomas et al. 1996	0/19	Mean age 30.0 (95% CI:27.9-32.1)	Not indicated	Not indicated	United Kingdom

Source: Applicant's submission ISE (p. 42)

Reviewer's Comments:
As illustrated from the table above, there were three distinct populations:

- *Women of childbearing age undergoing cesarean delivery under neuraxial anesthesia*
- *Middle age or elderly patients involving general surgical procedures and cardiac procedures, which have a predominance of male patients*
- *Asian patients under neuraxial anesthesia as the studies were conducted in Asian countries*

There is no evidence to suggest that its efficacy would be affected by either of these demographics.

6.1.2.2 (b) (4)

(b) (4)

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6.1.3 Subject Disposition

For both indications, most studies did not report discontinuation rate. The Applicant did not conduct an analysis of pooled subjects who were discontinued from the trials.

Reviewer's Comments:
The most common reason for treatment discontinuation appeared to be hypertension for both indications.

6.1.4 Analysis of Primary Endpoint(s)

The applicant-defined primary endpoint from the ISE for the indication of treatment of hypotension associated with anesthesia was "*…to reverse clinically relevant hypotensive effects of anesthesia, in many instances defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline*."

For treatment of hypotension during anesthesia, the published 16 trials presented by the Applicant demonstrated the reversing of hypotension associated with anesthesia. Studies demonstrated that bolus at a range of 50 to 200 mcg increases MAP about 20 mm Hg in 30 to 150 seconds.

(b) (4)

The Applicant's proposed language for the product label related to clinical studies is as follows:

14 CLINICAL STUDIES

The evidence for the efficacy of (b) (4) is derived from the (b) (4). The literature support includes (b) (4) studies evaluating the use of intravenous phenylephrine to treat hypotension during anesthesia (b) (4) henylephrine (b) (4) has been shown to (b) (4) raise blood pressure when administered either as a bolus dose or by continuous infusion following the development of hypotension during anesthesia. (b) (4)

6.1.4.1 Treatment

From the ISE, the suggested primary endpoint by the Applicant is *"…to reverse clinically relevant hypotensive effects of anesthesia, in many instances defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline."*

Most of the active controlled studies submitted to support this indication suggest that ephedrine and phenylephrine have similar effects on blood pressure, but phenylephrine results in bradycardia and may decrease cardiac output.

It is noted that duration of the effect on blood pressure in the studies is variable.

Administration of phenylephrine by bolus or infusion will be discussed separately below in reference to the blood pressure as primary endpoint.

6.1.4.1.1 Bolus Injection

Six of the twelve studies that evaluated the effect of bolus injections of phenylephrine on hypotension provided data on change in MAP before and after administration (see the table below as summarized by the Applicant):

Table 5 MAP after Bolus Treatment of Phenylephrine

Reference	Δ MAP (mm Hg)	Time after PHE dose	PHE dose (mcg)
Goertz et al. 1993a	22	30	~148
Goertz et al. 1993b	23-30	60	~69-75
Schwinn and Reves 1989	11.6-18.0	40-50	50-200
Dyer et al. 2008	17	24-40	50-100 (repeated every minute as needed)

Dyer et al. 2009	25.7	61.8	80
Ishiyama et al. 2003	~19	150	~112

Source: Modified from Applicant's submission ISE (pp. 59-60)

As shown in the table above, the average increase in MAP in response to bolus with is about 20 mm Hg. The time to reach maximal vasopressor effect is relatively consistent across studies, typically 30 seconds to a minute.

Reviewer's comments:
It is difficult to determine if there was a dose response because of the variability in patient population, starting blood pressure, and other factors which were not standardized in the literature.

6.1.4.1.2 Continuous Infusion or Infusion after Bolus

Two studies of phenylephrine used a combination of bolus and continuous infusion to treat hypotension during anesthesia. Both reported on effects on systolic and diastolic blood pressures as the table below:

Table 6 SBP and DBP after Combined Bolus and Infusion Treatment of Phenylephrine

Citation	Δ SBP (mm Hg)	Δ DBP (mm Hg)	PHE Dose
Brooker et al. 1997	20	14	40 mcg bolus (followed by infusion with 0.5 mcg/kg/min)
Alahuhta et al. 1992	6	6	100 mcg bolus (followed by 16.7 mcg/min infusion)

Source: Modified from Applicant's submission ISE (p. 62)

The Applicant cited two studies of phenylephrine infusion to treat hypotension. Kwak et al. (2002) used a ~33 mcg/min infusion of phenylephrine to raise SAP to 30% and 50% above baseline (mean 95.3 ± 6.7 mm Hg). This resulted in an increase in SAP of 35.1 mm Hg (from baseline to 30% above) and 52.9 mm Hg (from baseline to 50% above). However, phenylephrine did not increase arterial blood pressure by more than 30% from baseline in one-third of patients.

In another study (Nygren et al. 2006), after MAP was stable at 65-75 mm Hg, the phenylephrine infusion rate was titrated to produce a target MAP of 90 mm Hg (mean

0.5 ±0.22 mcg/kg/min). They reported a change in MAP from mean 68 ± 5 before phenylephrine administration to mean 92 ± 4 after, for a difference of 24 mm Hg.

Reviewer's Comments:

The suggested primary endpoint by the Applicant is "…to reverse clinically relevant hypotensive effects of anesthesia, in many instances defined as a drop in either systolic blood pressure or mean arterial pressure by 20% from baseline."

Bolus administration of phenylephrine (at dosing range of 50 to 150 mcg) increases MAP by about 20 mm Hg in 30 to150 seconds.

The data presented in the literature related to the treatment of hypotension associated with anesthesia suggests that phenylephrine reverses hypotension during anesthesia.

6.1.4.2 (b) (4)

(b) (4)

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In an active-controlled under neuraxial anesthesia for obstetric subjects, Mohta (et al., 2010) found that no difference between phenylephrine and mephentermine groups in incidence of hypotension (SBP < 80%) or < 100 mm Hg.

It must be noted that all three studies found no differences in fetal outcome in different doses or compared to the active comparator.

Reviewer's Comments:

The suggested primary endpoint by the Applicant is "… (b) (4)

The reported incidence of hypotension in the setting of anesthesia varies widely, with reports varying between 16 and 80%. The dosage of anesthetic agents, level of sensory blockade in the setting of neuraxial anesthesia, and the volume status of subjects are factors considered most likely to predict the occurrence of hypotension. However, these indices are neither sensitive nor specific as predictors of hypotension during anesthesia.

(b) (4)

(b) (4)

Unlike ephedrine, phenylephrine lacks direct inotropic effects. As a result, reflex bradycardia is common and treatment with an anticholinergic drug is sometime required. The decrease in heart rate appears to be dose dependent.

Using Doppler echocardiography to measure changes in cardiac output, Steward et al. (2010) also demonstrated that reduction in maternal cardiac output was directly attributable to the decrease in heart rate. Data from Robson et al. (1992) showed that maternal cardiac output correlates more closely with utero-placental blood flow than upper arm blood pressure measurement. The overall hemodynamic data suggest that

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant provided no analysis of secondary endpoints. However, heart rate is often reported in studies, but cardiac output (CO) was not measured in most studies.

Most studies report increase in the incidence of bradycardia. For the studies reported CO, most suggest a decrease in CO compared to placebo or active comparators such as ephedrine. Please see safety review for additional comments.

In most studies with cesarean section under neuraxial anesthesia, fetal outcome was measured by Apgar scores and fetal blood acid-base status.

Apgar score
When administered to treat anesthesia-induced hypotension, phenylephrine has no adverse effects on Apgar scores at one minute and five minutes after delivery as the tables below:

Table 11 Effects of Phenylephrine for Treatment of Maternal Hypotension on Apgar Scores

Citation	Number of PE-Treated Mothers	Apgar Scores	
Prakash et al. 2010	100 µg PE bolus, as needed: 30	At 1 min At 5 min At 10 min	Median (range) 9 (8-9) 10 (8-10) 10 (8-10)
Dyer et al. 2008	50-100 µg PE bolus, as needed: 10	At 1 min At 5 min	Median (range) 9 (7-9) 9 (9-10)
Thomas et al. 1996	100 µg PE bolus, as needed: 19	Number with Apgar <7 at 1min Number with Apgar <7 at 5 min	0 0
Kee et al. 2007	100 µg PE bolus, as needed: 74	Apgar scores were similar for the PE and ephedrine groups (data not provided).	
Moran et al. 1991	80-40 µg PE bolus, as needed: 31	Number with Apgar <7 at 1min Number with Apgar <9 at 5 min	0 0
LaPorta et al. 1995	40 µg PE bolus, as needed: 20	Number with Apgar <7 at 1min Number with Apgar <7 at 5 min	0 0
Dyer et al. 2009	80 µg PE bolus every minute: 20	At 1 min At 5 min	Median (range) 9 (6-9) 9.5 (9-10)

Source: Applicant's submission ISS (pp. 134-135)

When administered (b) (4) to treat hypotension associated with anesthesia, phenylephrine has no adverse effects on Apgar scores at one minute and five minutes after delivery as indicated the table below:

Table 12 Effects of Phenylephrine for (b) (4) of Maternal Hypotension on Apgar Scores

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status				
Tanaka et al. 2009	40 µg plus 10 µg bolus as needed: 50	Umbilical artery pH PCO_2 (kPa) PO_2 (kPa) HCO_3 (mmol/L) Base excess (mEq/L) Umbilical vein pH PCO_2 (kPa) PO_2 (kPa) HCO_3 (mmol/L) Base excess (mEq/L)		Mean ± SD 7.27 ± 0.05 7.5 ± 1.2 2.2 ± 0.76 25.3 ± 2.0 -2.7 ± 2.1 7.33 ± 0.05 6.1 ± 1.0 3.5 ± 0.9 23.4 ± 1.6 -2.2 ± 2.0		
Bjørnestad et al. 2009	40 µg bolus x 3: 20	Umbilical artery pH Umbilical vein pH		Mean ± SD 7.24 ± 0.11 7.30 ± 0.11		
Allen et al. 2010	25 µg: 20 50 µg: 20 75 µg: 19 100 µg: 22		**25 µg**	**50 µg**	**75µg**	**100µg**
		Umbilical artery pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mmol/L) Lactate (mmol/L) pH < 7.20	Mean ± SD 7.31 (7.29-7.31) 19.9 ± 4.8 52.3 ± 4.3 -1.8 ± 1.5 2.2 ± 0.5 0 (0%)	Mean ± SD 7.27 (7.25-7.30) 16.7 ± 5.7 56.7 ± 5.9 -2.0 ± 2.2 2.7 ± 0.8 0 (0%)	Mean ± SD 7.28 (7.23-7.30) 16.5 ± 4.9 59.3 ± 9.4 -2.5 ± 3.7 2.9 ± 1.6 2 (11)	Mean ± SD 7.26 (7.24-7.29) 16.9 ± 5.8 56.7 ± 6.8 -2.8 ± 2.0 2.6 ± 0.8 0 (0%)
		Umbilical vein pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mmol/L) Lactate (mmol/L)	7.35 (7.33-7.37) 27.1 ± 6.0 44.5 ± 4.3 -1.6 ± 1.4 1.9 ± 0.5	7.33 (7.32-7.35) 24.9 ± 4.5 45.7 ± 4.6 -1.8 ± 1.7 2.0 ± 0.6	7.33 (7.31-7.36) 25.1 ± 7.4 48.4 ± 8.9 -2.6 ± 3.2 2.4 ± 1.5	7.33 (7.30-7.35) 24.5 ± 5.5 47.1 ± 4.3 -2.2 ± 1.3 2.0 ± 0.5

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status			
Langesaeter et al. 2008	Bupivacaine 7 mg/ 0.25 µg/kg/min PE: 20 Bupivacaine 10 mg/ 0.25 µg/kg/min PE: 20		**B10/PE**	**B7/PE**	
		Umbilical artery	Mean (SEM)	Mean (SEM)	
		pH	7.26 (0.01)	7.29 (0.01)	
		Base excess	-2.3 (0.6)	-0.7 (0.4)	
		PCO_2	7.4 (0.3)	7.3 (0.2)	
		PO_2	1.8 (0.1)	2.2 (0.1)	
		Umbilical vein			
		pH	7.33 (0.01)	7.33 (0.01)	
		Base excess	-2.3 (0.4)	-1.3 (0.3)	
		PCO_2	6.1 (0.3)	5.8 (0.2)	
		PO_2	3.2 (0.2)	3.6 (0.2)	
Stewart et al. 2010	25 ug: 25 50 µg: 25 100 µg: 25		**25 µg**	**50 µg**	**100 µg**
			Mean ± SD	Mean ± SD	Mean ± SD
		Umbilical artery pH	7.31 ± 0.03	7.31 ± 0.04	7.30 ± 0.03
		Umbilical artery base excess	-0.9 ±1.6	-1.2 ±1.5	-1.2 ±1.5
		Umbilical vein pH	7.36 ± 0.02	7.35 ± 0.03	7.35 ± 0.03
		Umbilical vein base excess	-1.2 ± 1.6	-1.7 ± 1.1	-1.5 ± 1.3
Kee et al. 2008	100 µg/ml PE (100% PE): 24	Umbilical arterial	Median (interquartile range)		
		pH	7.29 (7.28-7.30)		
		pH < 7.2	0		
		PCO_2 (mm Hg)	53 (50-56)		
		PO_2 (mm Hg)	16 (14-19)		
		Base excess (mM)	-2.3 (-3.5 to -1.2)		
		Umbilical venous			
		pH	7.34 (7.33-7.35)		
		PCO_2 (mm Hg)	45 (42-49)		
		PO_2 (mm Hg)	27 (24-30)		
		Base excess (mM)	-2.7 (-3.4 to -1.3)		

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status			
Kee et al. 2004	PE to maintain SBP at 100% of baseline: 24 PE to maintain SBP at 90% of baseline: 25 PE to maintain SBP at 80% of baseline: 25		**Group 100**	**Group 90**	**Group 80**
		Umbilical arterial blood gases	Mean (SD)	Mean (SD)	Mean (SD)
		pH	7.30 (0.03)	7.30 (0.03)	7.32 (0.04)
		PCO_2 (kPa)	7.4 (0.7)	7.4 (0.6)	7.0 (0.6)
		PO_2 (kPa)	1.7 (0.7)	1.9 (0.4)	2.1 (0.6)
		Base excess (mmol/L)	-2.3 (2.6)	-1.8 (1.6)	-1.9 (2.2)
		Umbilical venous blood gases			
		pH	7.36 (0.04)	7.36 (0.03)	7.37 (0.03)
		PCO_2 (kPa)	5.9 (0.6)	5.9 (0.5)	5.7 (0.4)
		PO_2 (kPa)	3.4 (0.8)	3.4 (0.7)	3.7 (0.5)
		Base excess (mmol/L)	-1.9 (2.4)	-1.8 (1.7)	-1.6 (2.7)
		Fetal acidosis (umbilical artery pH <7.2)	0	0	0
Mohta et al. 2010	50 µg/ml PE: 30	Umbilical arterial blood gas	Mean (SD)		
		PO_2 (kPa)	4.3 (0.7)		
		PCO_2 (kPa)	5.1 (1.1)		
		pH	7.30 (0.03)		
		Base deficit (mmol/L)	6.3 (3.5)		
		Umbilical venous blood gases			
		PO_2 (kPa)	5.6 (0.9)		
		PCO_2 (kPa)	4.1 (0.7)		
		pH	7.38 (0.05)		
		Base deficit (mmol/L)	5.1 (4.5)		
Van Elsen et al. 2009	20 µg/ml PE: 4949	Umbilical blood gases were equal in both the PE and ephedrine groups.			

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status		
Ansari et al. 2011	Group 50 µg: 54 Group 100 µg: 63		**Group 50 µg**	**Group 100 µg**
		Umbilical arterial blood gases	Mean (SD)	Mean (SD)
		pH	7.31 (0.04)	7.30 (0.04)
		PCO_2 (mmHg)	52.5 (6.7)	55.4 (7.1)
		PO_2 (mmHg)	13.8 (5.0)	12.7 (5.4)
		Base excess (mmol/L)	-0.15 (2.5)	0.26 (1.9)
		Umbilical venous blood gases		
		pH	7.36 (0.03)	7.35 (0.03)
		PCO_2 (mmHg)	43.1 (4.2)	44.4 (5.2)
		PO_2 (mmHg)	23.8 (5.5)	24.4 (6.1)
		Base excess (mmol/L)	-1.5 (1.6)	-1.3 (1.6)
de Souza et al. 2011	100 µg/min PE plus 8 mg bupivacine: 30 100 µg/min PE plus 12 mg bupivacine: 30	Umbilical arterial blood gases	**Group 8**	**Group 12**
		pH	7.33 ± 0.04	7.33 ± 0.04
		PCO_2 (mmHg)	45.9 ± 6.9	45.8 ± 8.1
		Bicarbonate (mmol/L)	23.8 ± 2.0	24 ± 4.5
		Base excess (mmol/L)	-1.3 ± 1.7	-1.2 ± 1.4
		Arterial lactate (mmol/L)	1.9 ± 0.5	1.8 ± 0.4
		Umbilical venous blood gases		
		pH	7.35 ± 0.05	7.35 ± 0.04
		PCO_2 (mmHg)	42.7 ± 6.9	42.7 ± 6.1
		Bicarbonate (mmol/L)	22.8 ± 1.9	23.6 ± 3.4
		Base excess (mmol/L)	-2.1 ± 1.7	-1.7 ± 1.3
		Venous lactate (mmol/L)	1.9 ± 0.6	1.8 ± 0.4
		Fetal acidosis (pH <7.2)	0 (0%)	0 (0%)

Source: Applicant's submission ISS (pp. 131-133)

Reviewer's comments:
In the placebo-controlled study (Langesaeter et al., 2008), phenylephrine has not shown difference in Apgar scores compared to placebo.

Fetal Acidosis
Several studies evaluated fetal acid-base status in addition to Apgar scores to evaluate potential adverse effects of phenylephrine on the fetus.

Studies which used phenylephrine to treat hypotension as tables below all reported no evidence of fetal acidosis.

Table 13 Effect of Phenylephrine for Treatment of Maternal Hypotension on Measures of Fetal Blood Acid-base

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status	
Prakash et al. 2010	100 µg PE bolus, as needed: 30	Umbilical arterial acid-base status pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mEq/L) Umbilical venous acid-base status pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mEq/L)	Mean ± SD 7.32 ± 0.04 18.13 ± 3.21 43.50 ± 5.29 -1.61 ± 1.04 Mean ± SD 7.38 ± 0.05 28.1 ± 3.62 36.0 ± 4.72 -1.1 ± 1.12
Dyer et al. 2008	50-100 µg PE bolus, as needed: 10	Umbilical arterial pH Base deficit	Median (range) 7.28 (7.19-7.31) Mean (SD) -3.1 (1.9)
Thomas et al. 1996	100 µg PE bolus, as needed: 19	Umbilical artery blood gases pH PO2 (kPa) PCO2 (kPa) HCO3 (mmol/L) BE (mmol/L)	Mean (95% CI) 7.29 (7.28-7.30) 2.5 (2.2-2.8) 6.7 (6.4-6.9) 23.4 (22.8-23.9) -2.0 (-2.6-(-)1.4)
Kee et al. 2007	100 µg PE bolus, as needed: 74	 Umbilical arterial lactate (mmol/L) Umbilical venous lactate (mmol/L) Umbilical arterial PO2 (kPa) Umbilical venous PO2 (kPa) Umbilical artery pH Umbilical artery base excess (mmol)	Median 2.3 2.2 2.2 3.9 7.29 -2.6

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status	
Moran et al. 1991	80-40 µg PE bolus, as needed: 31	Umbilical artery	Mean ± SEM
		pH	7.32 ± 0.01
		PCO2 (mmHg)	52.1 ± 1.3
		PO2 (mmHg)	21.0 ± 2.1
		Base deficit (meq)	0.38 ± 0.35
		Umbilical vein	
		pH	7.36 ± 0.01
		PCO2 (mmHg)	43.7 ± 1.0
		PO2 (mmHg)	29.6 ± 1.5
		Base deficit (meq)	0.33 ± 0.22
Pierce et al. 1994	40 µg/mL PE, as needed: 13	Umbilical artery	Mean ± SD
		pH	7.31 ± 0.03
		PO2 (mmHg)	16.9 ± 4.9
		PCO2 (mmHg)	54.0 ± 6.1
		Umbilical vein	
		pH	7.36 ± 0.02
		PO2 (mmHg)	29.6 ± 8.8
		PCO2 (mmHg)	44.8 ± 4.6
LaPorta et al. 1995	40 µg PE bolus, as needed: 20	Umbilical vein	Mean ± SD
		pH	7.37 ± 0.03
		PO2 (kPa)	3.89 ± 1.05
		PCO2 (lPa)	5.57 ± 0.70
		Base excess (mmol/L)	0.7 ± 1.2
		Umbilical artery	
		pH	7.32 ± 0.05
		PO2 (kPa)	2.64 ± 1.05
		PCO2 (lPa)	6.68 ± 0.92
		Base excess (mmol/L)	0.9 ± 1.7

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status	
Dyer et al. 2009	80 µg PE bolus every minute: 20		Mean ± SD
		Umbilical arterial pH	7.31 ± 0.04
		Umbilical arterial PCO2 (kPa)	6.98 ± 1.12
		Umbilical arterial PO2 (kPa)	1.59 ± 0.39
		Umbilical arterial standard bicarbonate (mmol/L)	21.28 ± 2.45
		Umbilical arterial base excess (mmol/L)	-1.34 ± 3.06

Source: Applicant's submission ISS (pp. 140-142)

Studies which administered phenylephrine to treat hypotension associated with anesthesia reported no evidence of fetal acidosis.

Table 14 Effect of Phenylephrine for (b) (4) of Maternal Hypotension on Measures of Fetal Blood Acid-base

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status				
Tanaka et al. 2009	40 µg plus 10 µg bolus as needed: 50	Umbilical artery pH PCO_2 (kPa) PO_2 (kPa) HCO_3 (mmol/L) Base excess (mEq/L) Umbilical vein pH PCO_2 (kPa) PO_2 (kPa) HCO_3 (mmol/L) Base excess (mEq/L)		Mean ± SD 7.27 ± 0.05 7.5 ± 1.2 2.2 ± 0.76 25.3 ± 2.0 -2.7 ± 2.1 7.33 ± 0.05 6.1 ± 1.0 3.5 ± 0.9 23.4 ± 1.6 -2.2 ± 2.0		
Bjørnestad et al. 2009	40 µg bolus x 3: 20	Umbilical artery pH Umbilical vein pH		Mean ± SD 7.24 ± 0.11 7.30 ± 0.11		
Allen et al. 2010	25 µg: 20 50 µg: 20 75 µg: 19 100 µg: 22		**25 µg**	**50 µg**	**75µg**	**100µg**
		Umbilical artery pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mmol/L) Lactate (mmol/L) pH < 7.20	Mean ± SD 7.31 (7.29-7.31) 19.9 ± 4.8 52.3 ± 4.3 -1.8 ± 1.5 2.2 ± 0.5 0 (0%)	Mean ± SD 7.27 (7.25-7.30) 16.7 ± 5.7 56.7 ± 5.9 -2.0 ± 2.2 2.7 ± 0.8 0 (0%)	Mean ± SD 7.28 (7.23-7.30) 16.5 ± 4.9 59.3 ± 9.4 -2.5 ± 3.7 2.9 ± 1.6 2 (11)	Mean ± SD 7.26 (7.24-7.29) 16.9 ± 5.8 56.7 ± 6.8 -2.8 ± 2.0 2.6 ± 0.8 0 (0%)
		Umbilical vein pH PO_2 (mm Hg) PCO_2 (mm Hg) Base excess (mmol/L) Lactate (mmol/L)	7.35 (7.33-7.37) 27.1 ± 6.0 44.5 ± 4.3 -1.6 ± 1.4 1.9 ± 0.5	7.33 (7.32-7.35) 24.9 ± 4.5 45.7 ± 4.6 -1.8 ± 1.7 2.0 ± 0.6	7.33 (7.31-7.36) 25.1 ± 7.4 48.4 ± 8.9 -2.6 ± 3.2 2.4 ± 1.5	7.33 (7.30-7.35) 24.5 ± 5.5 47.1 ± 4.3 -2.2 ± 1.3 2.0 ± 0.5

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status			
Langesaeter et al. 2008	Bupivacaine 7 mg/ 0.25 µg/kg/min PE: 20 Bupivacaine 10 mg/ 0.25 µg/kg/min PE: 20		**B10/PE**	**B7/PE**	
		Umbilical artery	Mean (SEM)	Mean (SEM)	
		pH	7.26 (0.01)	7.29 (0.01)	
		Base excess	-2.3 (0.6)	-0.7 (0.4)	
		PCO_2	7.4 (0.3)	7.3 (0.2)	
		PO_2	1.8 (0.1)	2.2 (0.1)	
		Umbilical vein			
		pH	7.33 (0.01)	7.33 (0.01)	
		Base excess	-2.3 (0.4)	-1.3 (0.3)	
		PCO_2	6.1 (0.3)	5.8 (0.2)	
		PO_2	3.2 (0.2)	3.6 (0.2)	
Stewart et al. 2010	25 ug: 25 50 µg: 25 100 µg: 25		**25 µg**	**50 µg**	**100 µg**
			Mean ± SD	Mean ± SD	Mean ± SD
		Umbilical artery pH	7.31 ± 0.03	7.31 ± 0.04	7.30 ± 0.03
		Umbilical artery base excess	-0.9 ±1.6	-1.2 ±1.5	-1.2 ±1.5
		Umbilical vein pH	7.36 ± 0.02	7.35 ± 0.03	7.35 ± 0.03
		Umbilical vein base excess	-1.2 ± 1.6	-1.7 ± 1.1	-1.5 ± 1.3
Kee et al. 2008	100 µg/ml PE (100% PE): 24	Umbilical arterial	Median (interquartile range)		
		pH	7.29 (7.28-7.30)		
		pH < 7.2	0		
		PCO_2 (mm Hg)	53 (50-56)		
		PO_2 (mm Hg)	16 (14-19)		
		Base excess (mM)	-2.3 (-3.5 to -1.2)		
		Umbilical venous			
		pH	7.34 (7.33-7.35)		
		PCO_2 (mm Hg)	45 (42-49)		
		PO_2 (mm Hg)	27 (24-30)		
		Base excess (mM)	-2.7 (-3.4 to -1.3)		

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status			
Kee et al. 2004	PE to maintain SBP at 100% of baseline: 24 PE to maintain SBP at 90% of baseline: 25 PE to maintain SBP at 80% of baseline: 25		**Group 100**	**Group 90**	**Group 80**
		Umbilical arterial blood gases	Mean (SD)	Mean (SD)	Mean (SD)
		pH	7.30 (0.03)	7.30 (0.03)	7.32 (0.04)
		PCO_2 (kPa)	7.4 (0.7)	7.4 (0.6)	7.0 (0.6)
		PO_2 (kPa)	1.7 (0.7)	1.9 (0.4)	2.1 (0.6)
		Base excess (mmol/L)	-2.3 (2.6)	-1.8 (1.6)	-1.9 (2.2)
		Umbilical venous blood gases			
		pH	7.36 (0.04)	7.36 (0.03)	7.37 (0.03)
		PCO_2 (kPa)	5.9 (0.6)	5.9 (0.5)	5.7 (0.4)
		PO_2 (kPa)	3.4 (0.8)	3.4 (0.7)	3.7 (0.5)
		Base excess (mmol/L)	-1.9 (2.4)	-1.8 (1.7)	-1.6 (2.7)
		Fetal acidosis (umbilical artery pH <7.2)	0	0	0
Mohta et al. 2010	50 µg/ml PE: 30	Umbilical arterial blood gas	Mean (SD)		
		PO_2 (kPa)	4.3 (0.7)		
		PCO_2 (kPa)	5.1 (1.1)		
		pH	7.30 (0.03)		
		Base deficit (mmol/L)	6.3 (3.5)		
		Umbilical venous blood gases			
		PO_2 (kPa)	5.6 (0.9)		
		PCO_2 (kPa)	4.1 (0.7)		
		pH	7.38 (0.05)		
		Base deficit (mmol/L)	5.1 (4.5)		
Van Elsen et al. 2009	20 µg/ml PE: 4949	Umbilical blood gases were equal in both the PE and ephedrine groups.			

Citation	Number of PE-Treated Mothers	Measures of Fetal Blood Acid-base Status		
Ansari et al. 2011	Group 50 µg: 54 Group 100 µg: 63		**Group 50 µg**	**Group 100 µg**
		Umbilical arterial blood gases	Mean (SD)	Mean (SD)
		pH	7.31 (0.04)	7.30 (0.04)
		PCO_2 (mmHg)	52.5 (6.7)	55.4 (7.1)
		PO_2 (mmHg)	13.8 (5.0)	12.7 (5.4)
		Base excess (mmol/L)	-0.15 (2.5)	0.26 (1.9)
		Umbilical venous blood gases		
		pH	7.36 (0.03)	7.35 (0.03)
		PCO_2 (mmHg)	43.1 (4.2)	44.4 (5.2)
		PO_2 (mmHg)	23.8 (5.5)	24.4 (6.1)
		Base excess (mmol/L)	-1.5 (1.6)	-1.3 (1.6)
de Souza et al. 2011	100 µg/min PE plus 8 mg bupivacine: 30 100 µg/min PE plus 12 mg bupivacine: 30	Umbilical arterial blood gases	**Group 8**	**Group 12**
		pH	7.33 ± 0.04	7.33 ± 0.04
		PCO_2 (mmHg)	45.9 ± 6.9	45.8 ± 8.1
		Bicarbonate (mmol/L)	23.8 ± 2.0	24 ± 4.5
		Base excess (mmol/L)	-1.3 ± 1.7	-1.2 ± 1.4
		Arterial lactate (mmol/L)	1.9 ± 0.5	1.8 ± 0.4
		Umbilical venous blood gases		
		pH	7.35 ± 0.05	7.35 ± 0.04
		PCO_2 (mmHg)	42.7 ± 6.9	42.7 ± 6.1
		Bicarbonate (mmol/L)	22.8 ± 1.9	23.6 ± 3.4
		Base excess (mmol/L)	-2.1 ± 1.7	-1.7 ± 1.3
		Venous lactate (mmol/L)	1.9 ± 0.6	1.8 ± 0.4
		Fetal acidosis (pH <7.2)	0 (0%)	0 (0%)

Source: Applicant's submission ISS (pp. 136-139)

Reviewer's comments:
In the controlled studies, phenylephrine has not shown difference in Apgar score (Langesaeter et al., 2008), nor in fetal acidosis (Allen et al., 2010) compared to the placebo.

The Division consulted the Division of Bone, Reproductive, and Urologic Products (DBRUP) regarding the fetal outcome. Drs. Barbara Wesley, Christina Chang, and Audrey Gassman provided the following comments:

With the use of four different phenylephrine infusion rates in low-risk parturients (25, 50, 75, and 100 mcg/min), Allen et al. did not observe any differences among the groups with respect to: Apgar scores at 1 and 5 minutes, umbilical cord blood gases, incidence of fetal acidosis (umbilical artery pH < 7.2), and umbilical artery base excess. These findings were consistent with those reported by Stewart et al., who compared phenylephrine infusion rates at 25, 50, and 100 mcg/min.

Reviewer's comments:
Based on reviewing the Applicant's analysis, and the DBRUP consultation, the Apgar scores and fetal acid-base results suggest that phenylephrine has no adverse effects on fetal outcome.

In the two placebo-controlled studies (Allen, et al. 2010 and Langesaeter. et al., 2008), there were no difference in Apgar scores, and fetal acidosis between (b) (4) *phenylephrine vs. placebo.*

6.1.6 Other Endpoints

No other endpoints were analyzed by the Applicant.

6.1.7 Subpopulations

The Applicant's proposed language for the product label related special is as follows:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate or well-controlled studies (b) (4) phenylephrine hydrochloride in pregnant women (b) (4) animals. It is not known whether (b) (4) can cause fetal harm when administered to a pregnant woman (b) (4) should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

(b) (4)

6.1.7.1 Treatment

The 16 publications to support the indication of treatment did not distinguish between gender, age or race. However, comparing results among publications allows for some consideration of effects in subpopulations.

It is possible to contrast results within three general groups of subjects as follows:

- About half of the studies were restricted to women undergoing Cesarean deliveries
- A few of the studies included significant numbers of elderly subjects
- The results from studies conducted in Asia

6.1.7.1.1 Gender

Eleven studies identified that used phenylephrine to treat anesthesia-induced hypotension were conducted in women undergoing Cesarean deliveries. The efficacy in term of increasing SBP and MAP in these 11 studies seems to be no different from the studies in non-obstetric indications in which the contribution from male subjects was significant.

6.1.7.1.2 Age

The efficacy in term of increasing SBP and MAP in studies that included older subjects seems to be not different from the remainder of studies in which younger adults predominated.

These 16 publications did not include pediatric patients. However, one study (Tanaka et al. 2003) in infants and young children with Tetralogy of Fallot demonstrated that phenylephrine pressor responses after infusion of between 40-130 mcg bolus were within the range seen in the studies of adults (mean arterial pressure increased from baseline by a mean of 19 mm Hg).

6.1.7.1.3 Race

The racial data were not specifically provided in any of the studies.

Reviewer's Comments:
Despite that the 16 publications to support the indication of treatment did not distinguish special populations; it appears that phenylephrine has no different pharmacological effects on gender, age and race.

6.1.7.2 (b) (4)

(b) (4)

(b) (4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

6. 1.8. 1 Treatment

The recommended labeling for use of phenylephrine to treat anesthesia-induced hypotension is as follows:

- For bolus injection: 40 mcg to 100 mcg, not to exceed 200 mcg, doses to be administered every 1-2 minutes as needed
- For intravenous infusion: 10 mcg/min to 35 mcg/min starting dose, titrating to effect, not to exceed 200 mcg

Bolus:

Studies of the bolus approach demonstrated modest blood pressure responses (approximately 10-30 mm Hg) within relatively short periods of time (0.5-2 minutes), and with a modest dosing range (50- 200 mcg) as the table below by the Applicant.

Table 15 Blood Pressure Response to Phenylephrine IV Bolus for the Indication of Treatment

Reference	Blood pressure just prior to PHE	Blood pressure after PHE application	Δ BP (mm Hg)	Time after PHE dose	PHE dose
Schwinn and Reves 1989	MAP no baseline provided	NA	11.2 mm Hg 14.6 mm Hg 14.7 mm Hg 18.0 mm Hg	40 sec 40 sec 40 sec 40 sec	50 mcg 100 mcg 150 mcg 200 mcg
Goertz et al. 1993b	MAP 69-71 mm Hg	MAP 94-99 mm Hg	23-30 mm Hg	60 sec	~69-75 mcg[a]
Goertz et al. 1993a	61 mm Hg	83 mm Hg	22 mm Hg	30 sec	~ 148 µg[b]
Prakash et al. 2010	SBP 108 mm Hg	SBP 118 mm Hg	10 mm Hg	2 min	100 mcg

Dyer et al. 2008[c]	MAP 91 mm Hg	MAP 108 mm Hg	17 mm Hg	Within 24 to 40 seconds of administration	50-100 mcg, repeated every minute as needed
Dyer et al. 2009	72.8 mm Hg	98.5 mm Hg	25.7 mm Hg[d]	61.8 sec	80 µg
Ishiyama et al. 2003	61 mm Hg	80 mm Hg	~ 19 mm Hg	2.5 min	~112 µg[e]

Source: Modified from Applicant's submission ISE (pp. 66- 67)

Reviewer's Comments:
The proposed bolus phenylephrine dose range of 40-100 mcg, not to exceed 200 mcg seems to be acceptable to reverse hypotension during anesthesia.

.

The frequency of repeat dosing, every 1-2 minutes as needed, was a common feature of several of the 16 studies (das Neves et al. 2010, Dyer et al. 2008, Dyer et al. 2009); other studies noted the use of repeat doses as needed but did not specify a time range (George et al. 2010, Moran et al. 1991, Prakash et al. 2010).

Infusion:
Three studies of the continuous infusion approach to treating anesthesia-induced hypotension demonstrated modest blood pressure responses (6-24 mm Hg) (Nygren et al. 2006, Brooker et al. 1997, Alahuta et al. 1992) into a desired range as the table below by the Applicant.

Table 16 Blood Pressure Response to Phenylephrine IV Infusion for the Indication of Treatment

Citation	Baseline (mm Hg)	Post-dose (mm Hg)	Response (mm Hg)	Time of Post-dose Evaluation	PHE Dose
Nygren et al. 2006	MAP 68 ± 3	MAP 92 ± 4	24	NA	~35 µg/min (estimated from mean subjects' weight)
Brooker et al. 1997	SBP 120	SBP 144	20	NA	40 mcg bolus (followed by infusion with 0.5
Alahuhta et al. 1992	SBP 109	SBP 115	6	NA	100 mcg bolus (followed by 16.7 mcg/min infusion)

Source: Modified from Applicant's submission ISE (p. 68)

It must also be noted that two of the three studies described above also used an initial phenylephrine bolus administration, such that the continuous infusion likely represents an attempt to both achieve and maintain blood pressure within the desired range.

The Applicant's proposed language for the product label related to dosing for treatment of hypotension and administration is as follows:

2 DOSAGE AND ADMINISTRATION

PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, [redacted] as [redacted] bolus or [redacted] continuous [redacted].

For the treatment of hypotension during anesthesia

[redacted] Initial dose 40 to 100 mcg; [redacted] administered every 1-2 minutes as needed; not to exceed 200 mcg. [redacted]

Intravenous infusion: Starting rate 10 to 35 mcg/min, [redacted] not to exceed 200 mcg/min. [redacted]

PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, [redacted] can be diluted [redacted] bolus [redacted] with normal saline or 5% dextrose in water [redacted]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

Reviewer's Comments:
The Applicant proposed infusion at starting rate 10 to 35 mcg/min, titrating to effect; not to exceed 200 mcg/min seems to be acceptable to reverse the hypotension during anesthesia

6.1.8.2 [redacted]

[redacted]

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6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As phenylephrine has a very short time of action on the vasculature itself, with maximal vasopressor effect typically lasting 30 to 45 seconds in duration, few studies have provided data to show persistence of efficacy and/or tolerance.

Reviewer's Comments:
Tolerance to phenylephrine's effects is not expected during the short-term use of this product.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Overall exposure with subjects of 502 for indication of treatment is adequate. Overall exposure with subjects of 1578 for indication (b) (4) is also adequate.

Overall safety characterization from literature:

- No deaths reported
- No SAES reported (not specified in publications)
- Limited reported / quantification of AEs
- No Lab tests reported
- Most obstetric studies have quantitative fetal outcome data

The safety data through literature are limited.

The literature, combined with an analysis of the information contained in the FDA's Adverse Event Reporting System (FAERS), which was performed by the Applicant and Agency's Division of Pharmacovigilance II (DPVII), formed the basis for characterizing the risk profile associated with the proposed use of phenylephrine.

In literature, the adverse events related to use of phenylephrine were found to be primarily related to its action as alpha adrenergic receptor agonist such as hypertension and bradycardia. Interestingly, hypertension and bradycardia are also the most commonly reported in FAERS data.

Phenylephrine lacks direct inotropic effects, as a result, reflex bradycardia is common, and cardiac output decreases despite increases blood pressure. Using Doppler echocardiography to measure changes in cardiac output, Steward et al. (2010) also

demonstrated that reduction in maternal cardiac output was directly attributable to the decrease in heart rate. It is established that maternal cardiac output correlates more closely with utero-placenta blood flow than upper arm blood pressure measurement.

Considering blood pressure as one of overall hemodynamic parameters, phenylephrine increases blood pressure during anesthesia. However, the overall hemodynamic data suggest that increasing blood pressure is at the expense of reducing heart rate, cardiac output and stroke volume.

Most of the reported AEs can be monitored and treated in the Peri-operative setting. However, although not identified by the Applicant, there were case reports of hypertensive crisis associated with phenylephrine in the obstetric population. One case (b) (4) resulted in a coronary artery dissection (see details in 7.3.4.). It must be emphasized that phenylephrine should not be given to everyone even though there is a perception all hemodynamic related AEs can be monitored.

Most obstetrics studies provided quantitative fetal outcome data. All studies suggest that phenylephrine has no adverse effects on fetal outcome, which is concurred by the consultation from Division of Bone, Reproductive, and Urologic Products (DBRUP).

The Applicant has proposed the following text for the safety section of the label:

4 CONTRAINDICATIONS
(b) (4)

5 WARNINGS AND PRECAUTIONS
(b) (4)
.
(b) (4) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

6 ADVERSE REACTIONS
Adverse reactions to (b) (4) are primarily attributable to excessive pharmacologic activity (b) (4)
.
Adverse reactions reported in published clinical studies, observational trials, and case reports of (b) (4) are listed below by body system.
(b) (4) Disorders: Reflex bradycardia, lowered cardiac output, ischemia, hypertension, arrhythmias
Nervous System Disorders: Headache, blurred vision, neck pain, tremors

Gastrointestinal Disorders: Epigastric pain, vomiting, nausea
Skin and Subcutaneous Tissue Disorders: Pruritis
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

7 DRUG INTERACTIONS

(b) (4)
(b) (4) pressor effect of (b) (4) is increased in patients receiving:

- Monoamine oxidase inhibitors (MAOI)
- Oxytocin and oxytocic drugs
- (b) (4)
- Tricyclic antidepressants
- Angiotensin, aldosterone

(b) (4)
The pressor effect of (b) (4) is decreased in patients receiving:

- α-adrenergic antagonists
- Phosphodiesterase Type 5 inhibitors
- Mixed α- and β-receptor antagonists
- Calcium channel blockers, such as nifedipine
- Benzodiazepines
- ACE inhibitors

Based on the review of the safety data, the risks of phenylephrine has been limited characterized in literature, but well complemented by FAERS. The AEs are mostly consistent with the drug's pharmacological action, and can be monitored and treated in the perioperative setting. The Applicant's labeling accurately and adequately described the product's safety profile although changes are recommended.

7.1 Methods

I reviewed the literature provided by the Applicant which captured safety information. Both the Applicant and Agency's DPVII in the Office of Surveillance and Epidemiology analyzed the FAERS data and I reviewed their summaries.

.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.1.1 Treatment
The Applicant submitted 18 studies to support the safety for the treatment of anesthesia-induced hypotension with intravenous phenylephrine. Please see the complete list of the 18 studies in Section 9, Appendix.

Reviewer's comments:

Although it is impossible to determine whether any patients participated in more than one of the studies, and some publications did not provide any safety data, the number of exposures should be adequate to identify any life-threatening or severe AEs that occur with the treatment administration in adults.

The literature-based safety data, along with data from post marketing surveillance, are expected to be adequate for performing a benefit: risk and for labeling the safety issues related to the use of the product.

7.1.1.2 (b) (4)

The Applicant submitted 26 studies to support the safety for the (b) (4) of anesthesia-induced hypotension with intravenous phenylephrine. In addition to the 19 studies discussed in efficacy review, the Applicant also included seven studies for the use of (b) (4) phenylephrine injection by intramuscular administration rather than by intravenous. Please see the complete list of the 26 studies in Section 9, Appendix.

Reviewer's comments:
Although it is impossible to determine whether any patients participated in more than one of the studies, and some publications did not provide any safety data, the number of exposures should be adequate to identify any life-threatening or severe AEs that occur with the (b) (4) administration in adults.

Although the Applicant identified four placebo-controlled studies which theoretically allow a quantification of AEs, compared to placebo, only one (Allen et al., 2010) of the four provided a somehow broad safety data.

The literature-based safety data, along with data from post marketing surveillance, are expected to be adequate for performing a benefit: risk and for labeling the safety issues related to the use of the product.

7.1.2 Categorization of Adverse Events

The Applicant grouped and categorized AEs by system organ class (SOC). As the events were reported in the literature and the original data could not be retrieved, the Applicant categorized the events as described in the publications to the best of their ability.

Reviewer's comments:
The Applicant was consistent in their classification of the AEs by SOC and preferred terms.

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

The Applicant pooled data across studies to the extent possible by the indication and attempted to estimate and compare incidence of AEs.

7.2 Adequacy of Safety Assessments

7.2 Adequacy of Safety Assessments

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

7.2.1.1 Treatment
A total of 502 patients were treated with phenylephrine in the 18 studies. These studies were all designed to evaluate control of blood pressure during surgical procedures and therefore represent acute exposures.

7.2.1.2 (b) (4)
A total of 1,578 patients were treated with phenylephrine in these 26 studies. These studies were all designed to evaluate control of blood pressure during surgical procedures.

It is noted that the 19 publications (b) (4) provide a total of 1073 patients exposure, and the additional seven via non-IV routes provide a total of 475 patients exposure.

The Applicant noted the following regarding the demographics:

> *Most studies were in adult women of child-bearing age and other adults.*
>
> *Studies were performed all around the world. Although racial demographic data were not included in any of the publications, it is very likely that several studies from the Asian (Kee et al. 2004 from China, Kee et al. 2008 from China, and Yoon et al. 2012) were either exclusively or highly-enriched for Asian patients.*

Reviewer's comments:
Overall exposure with subjects of 502 for indication of treatment is adequate. Overall exposure with subjects of 1578 (b) (4) *is also adequate.*

Although the safety database does not contain the amount of demographic information generally captured with clinical trials for which the full study reports are provided to the

Agency, there is adequate information available to characterize the overall risk of the product.

7.2.2 Explorations for Dose Response

7.2.2.1 Treatment

The Applicant noted one study (Schwinn and Reves 1989) which compared single bolus doses of phenylephrine (50, 100, 150 or 200 mcg) administered during general anesthesia for coronary artery graft surgeries. Decreases in heart rate, though not classified as bradycardia, were seen with the higher two doses.

7.2.2.2 [redacted] (b) (4)

The Applicant noted that three studies evaluated a range of phenylephrine doses given during elective Cesarean deliveries. Safety findings from these studies that have been attributed to a specific dose are shown in the table below.

Table 18 Number of Adverse Reactions by Dose in Literature Submitted to [redacted] (b) (4)

	Allen et al. 2010				Kee et al. 2008				Stewart et al. 2010		
	25 µg/min	50 µg/min	75 µg/min	100 µg/min	25 µg/min	50 µg/min	75 µg/min	100 µg/min	25 µg/min	50 µg/min	100 µg/min
	n = 20	n = 20	n = 19	n = 22	n = 24	n = 25	n = 24	n = 24			
Hypertension				15				12			
Bradycardia						1	1	3			
Bradycardia requiring glycopyrolate	3		6	7					2		
Nausea and vomiting					5		4				
Headache				1							
Neck pain				1							
Ventricular bigeminy		1									

Source: Applicant's submission ISS (p. 115)

Reviewer's comments:

Although the Applicant attempted to conduct an exploration for dose responses of AEs, the overall safety data are limited. Cardiovascular AEs such as hypertension and bradycardia appears to be dose-dependent as illustrated by Allen et al (2010).

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing of phenylephrine was performed by the Applicant or included in the literature.

7.2.4 Routine Clinical Testing

No routine clinical testing was performed by the Applicant or included in the literature.

Reviewer's comments:
Although there were no clinical testing data available, it must be acknowledged that this product is for acute use, and has long history of clinical use. Any effect may have on these parameters likely to have an impact on subjects' clinical outcomes which would likely have been discerned and captured in the literature.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Clinical Pharmacology review by Dr. David Lee.

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

Norepinephrine is one of common used pressors approved for perioperative hypotension other than phenylephrine made by West-Ward. The label for Levophed (Norepinephrine Bitartrate Injection) contains description of precaution and AEs similar this product.

The Precautions section of the Levophed label (norepinephrine; NDA 007513) contains the following wording:

> **Avoid Hypertension:** Because of the potency of LEVOPHED and because of varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, then every five minutes if administration is to be continued.
>
> The rate of flow must be watched constantly, and the patient should never be left unattended while receiving LEVOPHED. Headache may be a symptom of hypertension due to over dosage.

> **Site of Infusion:** Whenever possible, infusions of LEVOPHED should be given into a large vein, particularly an antecubital vein because, when administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is apparently very slight. Some authors have indicated that the femoral vein is also an acceptable route of administration. A catheter tie-in technique should be avoided, if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity. Therefore, one should avoid the veins of the leg in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions of LEVOPHED were given in an ankle vein.
>
> **Extravasation:** The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of LEVOPHED into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Blanching along the course of the infused vein, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

The Adverse Reactions section of the Levophed label (norepinephrine; NDA 007513) contains the following wording:

> Body As A Whole: Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.
> Cardiovascular System: Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias.
> Nervous System: Anxiety, transient headache.
> Respiratory System: Respiratory difficulty.
> Skin and Appendages: Extravasation necrosis at injection site.
> Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when LEVOPHED is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury. Gangrene of extremities has been rarely reported.

> Overdoses or conventional doses in hypersensitive persons (e.g., hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating, and vomiting.

Reviewer's comments:
The AEs associated with phenylephrine are similar to those associated with norepinephrine. It must be noted that norepinephrine is by far a more potent pressor than phenylephrine.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Treatment
There were no deaths in patients included in the 18 publications of the use of phenylephrine for the treatment of anesthesia-induced hypotension.

7.3.1.2 (b) (4)
There were no deaths in patients included in the 26 publications of the use of phenylephrine for the (b) (4) of anesthesia-induced hypotension.

7.3.2 Nonfatal Serious Adverse Events

The Applicant did not report on nonfatal serious adverse events.

In reviewing the literature, potentially life-threatening adverse events were reported; however, the articles generally did not specify whether these events met the regulatory criteria for being serious adverse events. These events included hypertension and arrhythmias, both of which are known pharmacological effects of phenylephrine.

7.3.3 Dropouts and/or Discontinuations

The Applicant did not report on or conduct an analysis of the dropouts and discontinuations. In reviewing the literature, it was noted that both these events were rarely reported. This is expected, given the acute use of the product in the surgical setting and the short duration of follow-up.

7.3.4 Significant Adverse Events

The Applicant identified a few events which are clinically important.

Two cardiovascular events have been reported from the (b) (4) literature. An event of ventricular bigeminy has been reported by Allen et al. (2010). Of 81 patients evaluated in this study, one patient in the phenylephrine 50 mcg/min dose group experienced an episode of ventricular bigeminy. The phenylephrine infusion was stopped but bigeminy persisted intraoperatively and resolved spontaneously in the intensive care unit.

In a placebo-controlled study of (b) (4) single-dose phenylephrine, injections (50, 100 or 200 mcg phenylephrine) were administered concomitantly with alkalized lidocaine directly to the epidural space (Cheng et al. 1999). One patient experienced severe hypertension (BP 212/146 mm Hg) and mental confusion after injection of 200 mcg phenylephrine. Droperidol was injected intravenously, and the patient gradually recovered without sequelae.

Pruritis was reported from a single study (Langesaeter et al., 2008). In this study 9 patients (11.3%) had severe pruritus and 59 patients (73.8%) had little or moderate pruritus. The distribution of pruritis amongst groups receiving phenylephrine (n = 40) and those receiving anesthetic alone (n = 40) was not presented, and the authors did not comment further on this finding.

(b) (4), phenylephrine was reported to associate with a case of Takotsubo cardiomyopathy and hemorrhagic pituitary apoplexia in a previously healthy woman undergoing spinal anesthesia for an elective cesarean delivery[7]. She became hypertensive (200/130 mmHg) and tachycardic (170/min) after receiving two doses of 50 mcg phenylephrine for (b) (4) hypotension from the spinal anesthesia.

Uncited by the Applicant, the literature search identified two cases of hypertensive emergency:

Used to treat the hypotension, phenylephrine was reported to associate with a case of hypertensive emergency in a healthy woman undergoing spinal anesthesia for an elective cesarean section at term. However, because she received both phenylephrine and ephedrine, the relative contribution of each vasopressor to her hypertensive episode cannot be ascertained[8]. Her induction of anesthesia was accompanied by an infusion of phenylephrine 100 mcg/min. Within five minutes, she became hypotensive (63/44 mmHg) though her heart rate remained normal (70 beats per minute). Despite being given 9 mg of ephedrine, her blood pressure remained 66/52 mmHg and her heart rate dropped to 30 beats per minute. She was then given another 15 mg of

[7] Zdanowicz JA et al. Arch Gynecol Obstel 2011; 283:687-694

[8] Newell CP et al. Anaesthesia 2011; 66:615-619

ephedrine and 600 mcg of atropine. She soon complained of chest pain and shortness of breath; with her blood pressure rising to 188/99 mmHg and heart rate 140 beats per minute, phenylephrine infusion was discontinued. A healthy male infant was delivered within 12 minutes of spinal injection. Cardiac work-up and subsequent urgent cardiac catheterization showed that the mother had had a coronary artery dissection.

Reviewer's comments:
These events emphasize the need for careful monitoring of an appropriated dose of phenylephrine preoperatively.

Although not identified by the Applicant, there were cases of hypertensive emergency. With the cases of hypertensive emergency (One case involving (b) (4) *infusion resulted in a coronary artery dissection), it must be emphasized that phenylephrine should not be given to everyone even though there is a perception all hemodynamic related AEs can be monitored.*

7.3.5 Submission Specific Primary Safety Concerns

None of the AE reported in the literature raised special safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Treatment
Few events were quantified from published studies. Adverse events have been tabulated in the table below provided by the Applicant:

Table 19 Number of Adverse Reactions from Literature Submitted to Support the Indication of Treatment

	Prakash et al. 2010		Dyer et al. 2008	Thomas et al. 1996		George et al. 2010	das Neves et al. 2010[c]	TOTAL
	PE-b[a] (n=30)	E[b] (n=30)	PE-b (n=10)	PE-b (n=19)	E (n=19)	PE-b (n=45)	PE-i/b[d] (n=120)	PE (n=224)
Adverse Event	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Bradycardia	5(17)			11(58)	2(11)	2(4)	1 (1)	21(9)
Hypertension			2(20)				1 (1)	3(2)
Headache			1(10)					1(1)

Nausea							26 (22)[e]	26 (12)
Vomiting							8 (7)[f]	8 (4)
Epigastric pain			1(10)					1(1)
Blurred vision			1(10)					1(1)
Treatment failure						1(2)		1(1)

[a] PE-b = bolus injection of phenylephrine
[b] E = ephedrine
[c] randomized treatment vs. prevention
[d] 40 subjects per group: prevention (infusion, denoted i), prevention (single bolus), treatment (single bolus)
[e] 4 events, prevention infusion; 6 events, prevention bolus; 16 events, bolus treatment
[f] 0 events, prevention infusion; 3 events, prevention bolus; 5 events, bolus treatment

Source: Applicant's submission ISS (p. 46)

7.4.1.2 (b) (4)

Few events were quantified from published studies. Adverse events have been tabulated from placebo-controlled studies and from non-placebo controlled in the two tables below provided by the Applicant:

Table 20 Number of Adverse Reactions from Placebo Controlled Studies Submitted (b) (4)

	Allen et al. 2010		Langesaeter et al. al 2008	El-Tahan 2011		Total
	PE-i[a] (n=81)	Pbo[b] (n=20)	PE-i (n=40) Pbo (n=40)	PE-b[c] (n=30)	Pbo (n=30)	PE = 151
Adverse Event	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Hypertension[d]	45(56)[e] 15(19)[f]	2(10)				60 (40)
Bradycardia	16(20)	1(5)				16 (11)
Intraoperative nausea	29(36)	7(35)				29 (19)
Hypotension-induced nausea	7(9)	7(35)				7 (5)
Headache	1(1)					1 (<1)
Ischemic episodes				mean 8.9 ± 1.1	1.8 ± 0.7	N/A
Pruritis (severe)			9(12)[g]			9 (6)[g]
Intraoperative vomiting	4(5)	2(10)				4 (3)
Neck pain	1(1)					1 (<1)
Ventricular bigeminy	1(1)					1 (<1)

[a] Phenylephrine infusion
[b] Placebo
[c] Phenylephrine bolus
[d] Includes reports of reactive hypertension
[e] Predelivery hypertension
[f] Postdelivery hypertension
[g] May include placebo-treated subjects

Source: Applicant's submission ISS (p. 108)

Table 21 Number of Adverse Reactions from Non-Placebo Controlled Studies Submitted (b) (4)

	Ansari et al. 2011	Cooper et al. 2012	Tanaka et al. 2009	Stewart et al. 2010	Pinto et al. 2008		Kee et al. 2008		Kee et al. 2004	Mohta et al. 2010		de Souza et al. 2011	TOTAL
	PE-i[a] (n=117)	PE-i (n=100)	PE-i (n=50)	PE-i (n=75)	PE-i (n=30)	E[b] (n=30)	PE-i (n=24)	E[c] (n=98)	PE-i (n=74)	PE-i (n=30)	M[d] (n=30)	PE-i (n=60)	PE n=560
Adverse Event	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Hypertension[e]			14(28)				12(50)	45(46)	15(20)	6(20)[f]			47(8)
Bradycardia	12(10)	2(2)		2(3)			3(13)	3(3)	16(22)	7(23)		9(15)	51(9)
Nausea		13(13)	11(22)			8(27)						1(2)	25(4)
Nausea and vomiting	4(3)								15(20)				19(3)
Tremors												10(17)	10(2)
Headache					3(10)	13(43)							3(<1)
Dyspnea												1(2)	1(<1)

[a] Phenylephrine infusion
[b] Ephedrine
[c] Alone or in combination with phenylephrine
[d] Mephentermine
[e] Includes reports of reactive hypertension
[f] Hypertension thought to be caused by atropine was observed in 2 additional patients.

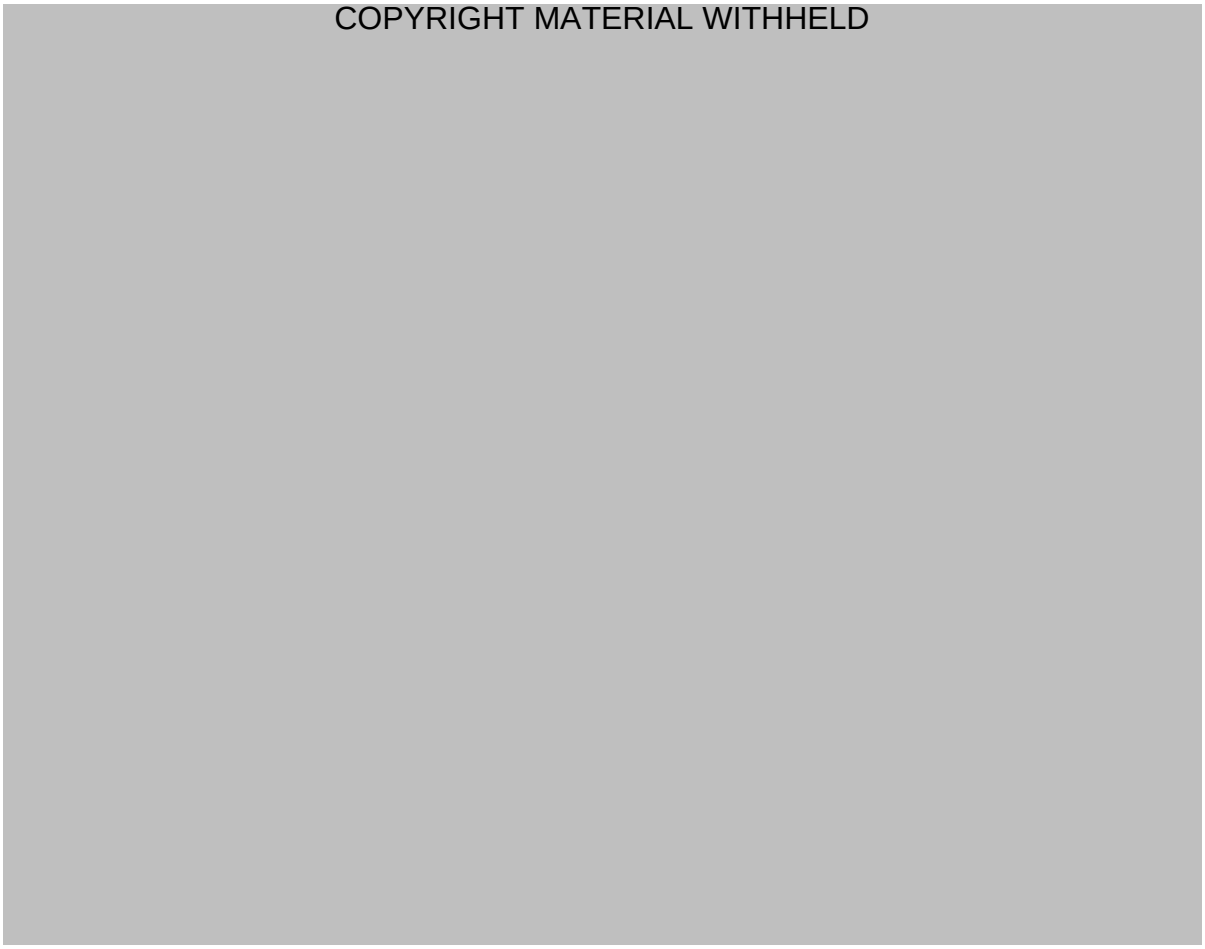
Source: Applicant's submission ISS (p.109)

The table of three placebo-controlled studies demonstrated that phenylephrine was associated with a higher frequency of hypertension and bradycardia than with placebo. From the two tables above, hypertension frequency ranged from 10%-56% in the eleven studies, and bradycardia ranged from 2%-23%.

Cardiac Output

In the placebo-controlled study by El-Tahan (2011), while phenylephrine increases MAP and decreases frequency of hypotension, it decreases the cardiac output as the figures below.

Figure 4 Cardiac Index after (b) (4) Phenylephrine (El-Tahan, 2011)



Cardiac index [CI] (l/min/m2) changes in the placebo (group 1) (n = 30), ephedrine 0.07 (group 2) (n = 30), 0.1 (group 3) (n = 30) and 0.15 mg/kg (group 4) (n = 30), and phenylephrine 1.5 µg/kg (Group 5) (n = 30) groups. Data are presented as mean ± S.D. P < 0.05 significant compared with * group 1 and † groups 2, 3, and 4.

In second placebo-controlled study (Langesaeter et al., 2008), phenylephrine did not significantly increase SBP (see efficacy review), but significantly decreases cardiac output as the figure blow.

Figure 5 Cardiac Output after (b) (4) Phenylephrine (Langesaeter et al., 2008)

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Cardiac Ischemia

In the same study by El-Tahan (2011), cardiac ischemic episodes (defined as ST-segment depression > 1 mm) were also more common with phenylephrine (El-Tahan 2011) as the table below.

Table 22 Cardiac Ischemia after (b) (4) Phenylephrine (El-Tahan, 2011)

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In the table above, the Group 1 represents placebo, Groups 2 to 4 represent three different doses of ephedrine, and group 5 represents phenylephrine.

It is interested in noting that while the frequency of hypotension decreases with phenylephrine (as discussed in efficacy review), the incidence of cardiac ischemia increases as illustrated in the table below:

Table 23 Frequency of Hypotension and Cardiac Ischemia after (b) (4) Phenylephrine (El-Tahan, 2011)

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With the increased cardiac ischemia as above, it is not surprised to note that the usage rescue nitroglycerine increased from 0 in placebo to 9 in phenylephrine.

Maternal Nausea and Vomiting

The cause of nausea and vomiting is difficult to assess since it is a common symptom of during anesthesia. Phenylephrine may directly cause nausea and vomiting, on the other hand, maintaining blood pressure preoperatively may potentially decrease nausea and vomiting.

In the placebo controlled study of Allen et al. (2010) the frequency of all perioperative nausea was the same in the phenylephrine (36%) and placebo (35%) groups, and all

perioperative vomiting was more common with placebo than phenylephrine (10% vs. 5%, respectively), suggesting that phenylephrine may not directly causing these gastrointestinal events. Since it was either not reduced or not eliminated despite increasing the blood pressure, the value of (b) (4) raising blood pressure may not outweigh associated risks

Kee et al. (2004) compared varying approaches to maintain blood pressure with phenylephrine (i.e., efforts to maintain systolic pressure within 80% of baseline, 90% of baseline, or 100% of baseline). Nausea and vomiting frequencies were greatest with the least effort to maintain baseline pressure (i.e., 40% frequency while maintaining pressure to 80% of baseline), intermediate with mid-level effort (16% frequency while maintaining pressure to 90% of baseline), and smallest with the greatest hemodynamic control (4% frequency while maintaining pressure to 100% of baseline). Kee's study suggests that phenylephrine was protective against these gastrointestinal effects.

Similar to Kee et al. (2004), Steward et al. (2010) found the incidences of nausea/vomiting correlated with control of hypotension; women administered the lowest phenylephrine infusion dose (25 mcg/min) had the highest incidence of hypotensive episodes and nausea/vomiting relative to those given phenylephrine at 50 or 100 mcg/min.

The interpretation of these findings should be considering the following issues:

- The trial was placebo-controlled.
- The number of women each arm was small.
- Nausea and vomiting were not assessed as primary endpoint.

Contrary to above two studies, in a dose-controlled study under neuraxial anesthesia, Tanaka et al.(2008) estimated ED95 of phenylephrine to be 159 mcg, but more nausea was reported in highest dose (110 mcg) arm.

Reviewer's comments:
The three placebo controlled studies (Imran et al., 2007, did not provide any safety data) provided the following common AEs by phenylephrine:

- *Nausea and vomiting*
- *Hypertension, bradycardia, cardiac ischemia, arrhythmia (ventricular bigeminy)*
- *Headache and neck pain*
- *Pruritis*

7.4.2 Laboratory Findings

No findings from routine labs were noted.

Reviewer's comments:
No routine labs were reported in the literature provided. This product has been used for decades as a pressor the product is used in acute setting. It is unlikely that the product alters routine labs in any clinically meaningful way.

7.4.3 Vital Signs

Blood pressure and heart rate are part of hemodynamic monitoring in all studies.

7.4.4 Electrocardiograms (ECGs)

The Applicant neither summarized nor analyzed the limited ECG information provided in literature except the cardiac ischemia (defined as ST-segment depression > 1 mm) by El-Tahan (2011) as discussed before.

7.4.5 Special Safety Studies/Clinical Trials

Cardiovascular Adverse Indices
As an adrenergic alpha receptor agonist, cardiovascular adverse events are expected. Bradycardia and hypertension are the most commonly reported AEs in the literature. Cardiac ischemia and arrhythmia are also reported. All those cardiovascular AEs have been discussed before, but will be summarized in this section again.

Hypertension:
As a presser, hypertension is consistent with the pharmacological effect of phenylephrine. Allen et al. (2010) reported a dose dependent maternal pre-delivery hypertension. There were cases of hypertensive emergency as described before. See Section 7.4.1 for detail.

Bradycardia:
Bradycardia is likely due to baroreceptor-mediated vagal stimulation, which is consistent with the pharmacological effect of phenylephrine. Bradycardia was observed in many studies. Again, Allen et al (2101) reported a dose dependent maternal pre-delivery bradycardia. See Section 7.4.1 for detail.

Cardiac ischemia:
El-Tahan (2011) reported phenylephrine increased in total time of intra-operative ischemia episode based on ST-T change and the rescue nitrate usage compare to placebo. It is interesting to note the author suggests that ephedrine even at the highest

dose studies produces less incidence of ischemia and requires less rescue nitrate usage. See Section 7.4.1 for detail.

Arrhythmia:
Allen et al. (2010) reported one case of ventricular bigeminy. Bradycardia is common AEs as described in detail in Section 7.4.1.

Maternal nausea and vomiting
There is no consistent evidence to support that phenylephrine decreases maternal intraoperative nausea and vomiting by maintaining blood. Please see Section 7.4.1 for detail.

Fetal Outcome
Please see efficacy review for details.

7.4.6 Immunogenicity

The Applicant provided no information regarding the immunogenicity of phenylephrine. None could be found in the literature. Phenylephrine is a simple, low molecular weight phenol derivative and is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

7.5.1.1 Treatment

One study compared single bolus doses of phenylephrine (50, 100, 150 or 200 mcg) administered during general anesthesia for coronary artery graft surgeries has been reported (Schwinn and Reves, 1989). Decreases in heart rate were seen with the higher two doses.

7.5.1.2 (b) (4)

Three studies which evaluated a range of phenylephrine doses given during elective Cesarean deliveries are summarized in the table below:

Table 24 Number of Adverse Reaction by Dose in Literature (b) (4)

	Allen et al. 2010				Kee et al. 2008				Stewart et al. 2010		
	25 µg/min	50 µg/min	75 µg/min	100 µg/min	25 µg/min	50 µg/min	75 µg/min	100 µg/min	25 µg/min	50 µg/min	100 µg/min
	n = 20	n = 20	n = 19	n = 22	n = 24	n = 25	n = 24	n = 24			
Hypertension				15				12			
Bradycardia						1	1	3			
Bradycardia requiring glycopyrolate	3		6	7					2		
Nausea and vomiting					5		4				
Headache				1							
Neck pain				1							
Ventricular bigeminy		1									

Source: Applicant's submission ISS (p. 115)

This table above suggests that hypertension and bradycardia are dose-dependent events.

Reviewer's comments:
Although the Applicant attempted to analyses the dose dependent AEs, it must be noted that the literature provided limited information on this matter.

7.5.2 Time Dependency for Adverse Events

The Applicant did not make assessment of the time dependency for adverse events. The literature did not provide information.

7.5.3 Drug-Demographic Interactions

The Applicant did not make assessment of the potential drug-demographic interactions. The literature did not provide information on this topic

7.5.4 Drug-Disease Interactions

The Applicant did not make assessment of the potential drug-disease interactions. The literature did not provide information on this topic.

Reviewer's comments:
The 120 day update provided a potential drug-disease interaction in Section 7.7 below.

7.5.5 Drug-Drug Interactions

The Applicant did not make assessment of the potential drug-drug interactions. The literature did not provide information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This product is indicated for acute use only. Therefore, carcinogenicity evaluations are not required.

7.6.2 Human Reproduction and Pregnancy Data

There appears to be no fetal safety signal in terms of Apgar score, fetal acidosis based on obstetric studies. However, no longer-term follow-up data on infants are available.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant provided no information regarding the effects of PHE on the growth of pediatric patients. Literature did not provide such effects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant provides no information regarding overdose, drug abuse potential.
As this product's vascular effects are very brief, the blood pressure returns rapidly to baseline values after infusions are stopped, withdrawal and rebound are unlikely.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day safety update, and provided one recent publication relevant to the safety.

Mohta et al. (2013) [9] present the case of a hypothyroid patient who developed recurrent episodes of hypotension after spinal anesthesia and showed an ill-sustained response to phenylephrine. The patient (age 26 and at full-term pregnancy) was scheduled for elective caesarean section under spinal anesthesia. She was known to be hypothyroid for 2 years and was being treated 50 mcg oral thyroxin daily. She developed hypotension two minutes after spinal injection, which was successfully treated with 100 mcg IV phenylephrine; however, the response was poorly sustained and further episodes of hypotension required additional boluses of 50-100 mcg phenylephrine at 7, 8, 12, 16, 18, 21, 24, and 26 minutes after spinal injection. The author discusses possible causes for the patient's poor response to phenylephrine, and concluded that even mildly hypothyroid patients undergoing caesarean section under spinal anesthesia may show persistent hemodynamic instability, which could be contributed to by reduced responsiveness to alpha-agonists or adrenocortical insufficiency.

Reviewer's comments:
Mohta et al. (2013) reports on a potential disease (hypothyroidism) and drug interaction.

8 Postmarket Experience

Applicant Reported Findings
The Applicant conducted a search of the Agency's Adverse Event Reporting System (AERS) database for adverse events associated with the use of phenylephrine through June 30, 2012.

It must be noted that since the submission of the NDA, the AERS has been converted to FAERS.

Adverse events were analyzed for phenylephrine administered intravenously as well as formulations defined as intraocular, inhaled/intranasal or uncertain parenteral. Events from oral formulations of phenylephrine were not evaluated. Subsets of each dataset included analyses of serious events, non-serious events, and fatal events.

This review only includes data from IV route of administration.

Adverse events with intravenous phenylephrine based on gender were constructed by the Applicant as the table below:

[9] Mohta M et al. Anaesthesia Intensive Care 2013; 41:683-684

Table 25 All AEs by IV Phenylephrine in AERS stratified by Gender

Number of All Adverse Events, All Suspect Mentions, by Gender		
Gender	**N**	**Percent of Total AEs**
Female	169	39.49%
Male	230	53.74%
Unknown	3	0.70%
Unspecified	26	6.07%
Total	**428**	**100.00%**

Source: Applicant's submission ISS (p. 155)

Adverse events with intravenous phenylephrine based on age were constructed by the Applicant as the table below:

Table 26 All AEs by IV Phenylephrine in AERS stratified by Age

Number of All Adverse Events, All Suspect Mentions, by Age		
Age	**N**	**Percent of Total AEs**
<2	0	0.00%
2-5	0	0.00%
6-17	12	2.80%
18-65	213	49.77%
>65	114	26.64%
Unknown	89	20.79%
Total	**428**	**100.00%**

Source: Applicant's submission ISS (p. 156)

Doses of administered intravenous phenylephrine were generally unknown, although for those cases that provided dose data the administered drug was mostly reported as greater than 1 mg. Adverse events with intravenous phenylephrine based on dose were constructed by the Applicant as the table below:

Table 27 All AEs by IV Phenylephrine in AERS stratified by Dose

Number of All Adverse Events by Dose, All Suspect Mentions		
Dose	**N**	**Percent of Total AEs**
51-100 µg	6	1.40%
101-200 µg	6	1.40%
201-500 µg	13	3.04%
501-1,000 µg	5	1.17%
>1 mg	75	17.52%
Other	103	24.07%
Unknown	220	51.40%
Total	**428**	**100.00%**

Source: Applicant's submission ISS (p. 155)

The table below includes adverse event summaries reported by system organ class and preferred term which was constructed by the Applicant:

Table 28 Summary of All IV Phenylephrine AEs reported in the AERS database

System Organ Class	Preferred Term	Number of Events
Blood and lymphatic system disorders	Coagulopathy	1
Blood and lymphatic system disorders	Idiopathic thrombocytopenic purpura	1
Blood and lymphatic system disorders	Thymus disorder	1
Blood and lymphatic system disorders	Thymus enlargement	1
Cardiac disorders	Acquired cardiac septal defect	1

System Organ Class	Preferred Term	Number of Events
Cardiac disorders	Acute left ventricular failure	1
Cardiac disorders	Acute myocardial infarction	1
Cardiac disorders	Arteriospasm coronary	4
Cardiac disorders	Atrial flutter	1

Cardiac disorders	Atrioventricular block complete	2
Cardiac disorders	Atrioventricular block second degree	1
Cardiac disorders	Bradycardia	17
Cardiac disorders	Cardiac arrest	6
Cardiac disorders	Cardiac failure congestive	1
Cardiac disorders	Cardiogenic shock	1
Cardiac disorders	Cardio-respiratory arrest	5
Cardiac disorders	Conduction disorder	1
Cardiac disorders	Coronary artery dissection	1
Cardiac disorders	Cyanosis	1
Cardiac disorders	Mitral valve incompetence	1
Cardiac disorders	Myocardial infarction	2
Cardiac disorders	Nodal arrhythmia	1
Cardiac disorders	Sinus tachycardia	1
Cardiac disorders	Stress cardiomyopathy	3
Cardiac disorders	Tachyarrhythmia	3
Cardiac disorders	Tachycardia	5
Cardiac disorders	Torsade de pointes	1
Cardiac disorders	Ventricular dysfunction	1
Cardiac disorders	Ventricular extrasystoles	1
Cardiac disorders	Ventricular hypokinesia	1
Cardiac disorders	Ventricular tachycardia	5

System Organ Class	**Preferred Term**	**Number of Events**
Congenital, familial and genetic disorders	Atrial septal defect	1
Eye disorders	Blindness	1
Gastrointestinal disorders	Nausea	1
General disorders and administration site conditions	Asthenia	2

General disorders and administration site conditions	Breakthrough pain	1
General disorders and administration site conditions	Chest discomfort	2
General disorders and administration site conditions	Chest pain	3
General disorders and administration site conditions	Condition aggravated	1
General disorders and administration site conditions	Death	1
General disorders and administration site conditions	Drug effect prolonged	1
General disorders and administration site conditions	Drug ineffective	6
General disorders and administration site conditions	Drug interaction	3
General disorders and administration site conditions	Feeling hot	1
General disorders and administration site conditions	General physical health deterioration	1
General disorders and administration site conditions	Inhibitory drug interaction	1
General disorders and administration site conditions	Injection site extravasation	1
General disorders and administration site conditions	Multi-organ failure	1
General disorders and administration site conditions	Necrosis	1

System Organ Class	**Preferred Term**	**Number of Events**
General disorders and administration site conditions	No therapeutic response	1
General disorders and administration site conditions	Nodule	1
General disorders and administration site conditions	Pain	1
General disorders and administration site conditions	Product container issue	1

General disorders and administration site conditions	Product quality issue	1
General disorders and administration site conditions	Pyrexia	1
General disorders and administration site conditions	Unevaluable event	1
Immune system disorders	Anaphylactic shock	1
Immune system disorders	Anaphylactoid shock	1
Immune system disorders	Drug hypersensitivity	1
Infections and infestations	Gangrene	1
Infections and infestations	Infection	1
Infections and infestations	Pilonidal cyst	1
Infections and infestations	Pneumonia	2
Infections and infestations	Sepsis	1
Infections and infestations	Septic shock	1
Infections and infestations	Superinfection	1
Injury, poisoning and procedural complications	Accidental overdose	1
Injury, poisoning and procedural complications	Anaesthetic complication	2
Injury, poisoning and procedural complications	Anaesthetic complication cardiac	1
Injury, poisoning and procedural complications	Delayed recovery from anaesthesia	1

System Organ Class	**Preferred Term**	**Number of Events**
Injury, poisoning and procedural complications	Device failure	3
Injury, poisoning and procedural complications	Device malfunction	1
Injury, poisoning and procedural complications	Drug administration error	5
Injury, poisoning and procedural complications	Drug dose omission	1

Injury, poisoning and procedural complications	Drug exposure during pregnancy	14
Injury, poisoning and procedural complications	Drug label confusion	1
Injury, poisoning and procedural complications	Incorrect dose administered	2
Injury, poisoning and procedural complications	Incorrect route of drug administration	1
Injury, poisoning and procedural complications	Injury	1
Injury, poisoning and procedural complications	Maternal exposure during pregnancy	3
Injury, poisoning and procedural complications	Medication error	4
Injury, poisoning and procedural complications	Operative haemorrhage	1
Injury, poisoning and procedural complications	Overdose	3
Injury, poisoning and procedural complications	Post procedural complication	4
Injury, poisoning and procedural complications	Procedural complication	3
Injury, poisoning and procedural complications	Recurrence of neuromuscular blockade	1
Injury, poisoning and procedural complications	Renal injury	1

System Organ Class	**Preferred Term**	**Number of Events**
Injury, poisoning and procedural complications	Toxicity to various agents	1
Injury, poisoning and procedural complications	Vasoplegia syndrome	1
Injury, poisoning and procedural complications	Wrong drug administered	3
Injury, poisoning and procedural complications	Wrong technique in drug usage process	1
Investigations	Blood creatine phosphokinase increased	4

Investigations	Blood creatine phosphokinase MB increased	4
Investigations	Blood creatinine increased	2
Investigations	Blood lactate dehydrogenase increased	2
Investigations	Blood lactic acid increased	3
Investigations	Blood pressure decreased	8
Investigations	Blood pressure diastolic decreased	1
Investigations	Blood pressure increased	2
Investigations	Blood pressure systolic increased	3
Investigations	Blood urea increased	1
Investigations	Cardiac enzymes increased	1
Investigations	Echocardiogram abnormal	1
Investigations	Ejection fraction decreased	3
Investigations	Electrocardiogram QT prolonged	2
Investigations	Electrocardiogram ST segment depression	1
Investigations	Electrocardiogram ST segment elevation	4
Investigations	Electrocardiogram T wave inversion	6

System Organ Class	**Preferred Term**	**Number of Events**
Investigations	Electrocardiogram U-wave abnormality	1
Investigations	Haemoglobin decreased	1
Investigations	Heart rate decreased	1
Investigations	Mean arterial pressure increased	1
Investigations	Myoglobin urine present	1
Investigations	Oxygen saturation decreased	2
Investigations	Troponin I increased	1
Investigations	Troponin increased	1

Metabolism and nutrition disorders	Enzyme abnormality	1
Metabolism and nutrition disorders	Fluid overload	1
Metabolism and nutrition disorders	Hyperglycaemia	2
Metabolism and nutrition disorders	Hyperkalaemia	1
Metabolism and nutrition disorders	Metabolic acidosis	8
Metabolism and nutrition disorders	Metabolic disorder	1
Metabolism and nutrition disorders	Propofol infusion syndrome	7
Musculoskeletal and connective tissue disorders	Muscular weakness	1
Musculoskeletal and connective tissue disorders	Neck pain	1
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	1
Nervous system disorders	Amnesia	1
Nervous system disorders	Anoxic encephalopathy	1
Nervous system disorders	Aphasia	7
Nervous system disorders	Brain oedema	1
Nervous system disorders	Cerebral atrophy	1
Nervous system disorders	Cerebral ventricle dilatation	3

System Organ Class	**Preferred Term**	**Number of Events**
Nervous system disorders	Cerebrovascular spasm	1
Nervous system disorders	CNS ventriculitis	1
Nervous system disorders	Coma	2
Nervous system disorders	Convulsion	1
Nervous system disorders	Depressed level of consciousness	1
Nervous system disorders	Encephalopathy	6
Nervous system disorders	Grand mal convulsion	3
Nervous system disorders	Haemorrhagic transformation stroke	1
Nervous system disorders	Headache	3

Nervous system disorders	Hydrocephalus	2
Nervous system disorders	Intracranial aneurysm	2
Nervous system disorders	Intracranial pressure increased	2
Nervous system disorders	Loss of consciousness	1
Nervous system disorders	Neuromyopathy	1
Nervous system disorders	Paraesthesia	1
Nervous system disorders	Posterior reversible encephalopathy syndrome	2
Nervous system disorders	Sedation	2
Nervous system disorders	Speech disorder	1
Nervous system disorders	Subarachnoid haemorrhage	2
Nervous system disorders	Syncope	1
Nervous system disorders	Syncope vasovagal	2
Nervous system disorders	Tremor	1
Nervous system disorders	Unresponsive to stimuli	6
Pregnancy, puerperium and perinatal conditions	Foetal disorder	1

System Organ Class	**Preferred Term**	**Number of Events**
Pregnancy, puerperium and perinatal conditions	Polyhydramnios	2
Pregnancy, puerperium and perinatal conditions	Premature labour	1
Pregnancy, puerperium and perinatal conditions	Uterine hypotonus	2
Psychiatric disorders	Anhedonia	1
Psychiatric disorders	Anxiety	3
Psychiatric disorders	Confusional state	4
Psychiatric disorders	Delirium	6
Psychiatric disorders	Depression	1
Psychiatric disorders	Fear	1

Psychiatric disorders	Mental status changes	4
Psychiatric disorders	Post-traumatic stress disorder	1
Renal and urinary disorders	Nephrogenic diabetes insipidus	1
Renal and urinary disorders	Oliguria	1
Renal and urinary disorders	Polyuria	1
Renal and urinary disorders	Renal failure	3
Renal and urinary disorders	Renal failure acute	2
Renal and urinary disorders	Renal tubular necrosis	1
Reproductive system and breast disorders	Priapism	1
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	1
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1
Respiratory, thoracic and mediastinal disorders	Apnoea	1
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1

System Organ Class	**Preferred Term**	**Number of Events**
Respiratory, thoracic and mediastinal disorders	Epistaxis	1
Respiratory, thoracic and mediastinal disorders	Increased bronchial secretion	1
Respiratory, thoracic and mediastinal disorders	Lung infiltration	9
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	5
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	1
Respiratory, thoracic and mediastinal disorders	Respiratory depression	2
Respiratory, thoracic and mediastinal disorders	Respiratory disorder	1

Skin and subcutaneous tissue disorders	Generalised erythema	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	2
Social circumstances	Disability	1
Surgical and medical procedures	Caesarean section	2
Surgical and medical procedures	Continuous haemodiafiltration	1
Surgical and medical procedures	Nerve block	2
Vascular disorders	Air embolism	2
Vascular disorders	Circulatory collapse	1
Vascular disorders	Haematoma	1
Vascular disorders	Hypertension	15
Vascular disorders	Hypertensive crisis	1
Vascular disorders	Hypoperfusion	1
Vascular disorders	Hypotension	10
Vascular disorders	Infarction	1
System Organ Class	**Preferred Term**	**Number of Events**
Vascular disorders	Peripheral ischaemia	1
Vascular disorders	Peripheral vascular disorder	1
Vascular disorders	Shock	2
Vascular disorders	Vascular occlusion	1
Total Events		**428**

Source: Applicant's submission ISS (pp. 164-174)

DPV II Findings-AERS Database

Drs. Argual and Gilbert at the DPV II conducted a review of the FAERS database, as well as literature, for adverse events related to the use of phenylephrine for the proposed indication.

The FAERS search was conducted on 12/30/2013, and covered the time period from January 1, 1969 to December 30, 2013. According the consultation, the FAERS search retrieved 137 reports. These are total counts of FAERS reports and may include

duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA.

The table below lists FAERS crude counts of Preferred Terms (PT) reported for phenylephrine HCl 1% injection. Preferred terms with N > 4 are sorted by decreasing number. Preferred terms with N < 3 were also evaluated; we did not identify any new safety signals among the remaining preferred terms.

Table 29 FAERS Crude Counts of Preferred Terms (Provided by DPVII)

Table 3.2. FAERS Crude Counts of Preferred Terms (N≥4) for Phenylephrine HCl 1% Injection as of December 30, 2013. Total Number of reports, N=137; Reports since June 21, 2012, N=16			
Preferred Term	**Count of PT (N) Total**	**Count of PT (N) since 6/21/2012**	**Appears in the Draft Label*^**
Maternal Exposure During Pregnancy	21	1	Yes. SP
Bradycardia	19	1	Yes. W/P, AR, OD
Hypertension	16	1	Yes. AR, OD
Hypotension	16	4	IR
Blood Pressure Decreased	9	3	IR
Lung Infiltration	9	0	No
Aphasia	7	0	No
Cardiac Arrest	7	0	No
Drug Ineffective	7	2	U
Encephalopathy	7	0	No
Medication Error	7	0	No
Delirium	6	0	No
Electrocardiogram T Wave Inversion	6	0	No
Metabolic Acidosis	6	0	No
Tachycardia	6	0	Yes. OD
Unresponsive To Stimuli	6	0	No

Table 3.2. FAERS Crude Counts of Preferred Terms (N≥4) for Phenylephrine HCl 1% Injection as of December 30, 2013. Total Number of reports, N=137; Reports since June 21, 2012, N=16			
Preferred Term	**Count of PT (N) Total**	**Count of PT (N) since 6/21/2012**	**Appears in the Draft Label*^**
Ventricular Tachycardia	6	0	Yes. OD
Cardio-Respiratory Arrest	5	0	No
Pulmonary Oedema	5	0	No
Stress Cardiomyopathy	5	0	No
Syncope	5	0	No
Anxiety	4	0	No
Arteriospasm Coronary	4	0	No

Blood Creatine Phosphokinase Increased	4	0	No
Blood Creatine Phosphokinase Mb Increased	4	0	No
Caesarean Section	4	2	PR
Chest Discomfort	4	0	No
Confusional State	4	0	No
Drug Interaction	4	3	Yes. W/P, DI
Headache	4	1	Yes. AR, OD
Mental Status Changes	4	0	No
Oxygen Saturation Decreased	4	2	No
Post Procedural Complication	4	0	PR

[*] Phenylephrine Hydrochloride Injection, USP, 1% 10 mg/mL, 1 mL single use vial, 5ml pharmacy bulk package vial, and 10ml pharmacy bulk package vial. Draft Package Insert – Content of Labeling. Annotated Draft Phenylephrine Hydrochloride Injection, USP Package Insert in PLR format. Eclat Pharmaceuticals, Chesterfield, MO 63005 USA. Revised September 2013.

[^] Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations: Other Categories: IR = Indication-related, PR = Procedure-related, U = Uninformative

DPVII Findings-Literature Search

On January 6, 2014, the DPV-2 conducted their literature search using PubMed to identify English-language literature using “phenylephrine”, “adverse”, “hypotension” as an unrestricted search terms.

Drs. Argual and Gilbert provide the comments as follows:

One article retrieved with the PubMed search (described above) describes Tako-tsubo (Broken Heart or Stress Cardiomyopathy) Syndrome in association with (b) (4) *an obstetric patient undergoing spinal anesthesia2. A number of articles pointed to maternal bradycardia in obstetric patients (see, for example, Cyna, AM et al.3); and, some articles referred to fetal acidosis though it is unclear whether this was associated with use of phenylephrine or the underlying maternal hypotension. An additional article summarized anaphylactic and allergic reactions with “sulfited” medications and included phenylephrine on the list.*

The majority of articles retrieved from PubMed focused on the efficacy of phenylephrine for use in hypotension associated with spinal anesthesia in obstetrics; others compared the efficacy of phenylephrine with that of ephedrine.

Consistent with the fact that phenylephrine is an older drug used via different routes for different purposes there are a number of published articles describing phenylephrine use in a variety of settings. These include: use in eye drops (to reverse ptosis caused by Botox), use as a decongestant and possible teratogenicity associated with this use in

pregnant women, use to reverse a hypothetical drug-induced priapism, and, topical use in nasal/sinus/other surgery and the possible development of hypertension.

Discussion and Conclusion from DPV II

Drs. Argual and Gilbert provide the discussion and conclusion as follows:

Our review examined all phenylephrine HCL 1% injection adverse events reported in FAERS and the published medical literature in an effort to provide a comprehensive overview of adverse events that could be used to identify new safety signals for labeling of this product.

Our review of all unlabeled adverse events did not find any events that were compelling enough to suggest a new safety signal or to require any addition to the proposed phenylephrine labeling. The search of the FAERS database retrieved 137 reports. There were 12 unique FAERS cases coded with an outcome of death. Analysis of these reports did not find any report of death causally linked to use of IV phenylephrine; nor were there any unique patterns of adverse events across age groups, gender, country of reporter, or location of use.

No safety risks were identified from FAERS and published medical literature suggesting the need to modify the proposed phenylephrine label at this time.

Reviewer's Comments:
I agree with the conclusion drawn by DPV-2 based on FAERS and literature. It must be noted that there were two cases of Torsade's reported in FAERS, but causality to phenylephrine could not be established.

9 Appendices

The Applicant listed all studies to support the safety for the indications of treatment and (b) (4) in the following two tables.

Table 30 Literature to Support the Safety for the Indication of Treatment

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Alahuhta et al. 1992 Finland	8 patients (8F) Mean 28.5 ± 3.3 years	Spinal anesthesia Elective Cesarean delivery	PE: Prophylactic 1 mL IV bolus was given, followed by continuous infusion of 10 mL/hour (1 mL = 100 µg) If SAP fell by >10mm Hg from baseline, bolus injections to supplement infusion was allowed.	Ephedrine (5 mg initial bolus and then as needed) N = 9 patients	Moderate systolic hypotension blood pressure <90 mm Hg in 1 subject
Brooker et al. 1997 United States	13 patients (10M/3F) Median 62.5 years (25-71)	Spinal anesthesia Elective surgery (5 orthopedic, 6 urologic, 2 gynecologic operations)	40 µg IV bolus when systolic pressure dropped by 15%, followed by infusion of 0.5 µg/kg/min. If needed, additional bolus doses could be given and infusion rate could be doubled. Total dose of PE ranged from 170-1,132 µg.	Epinephrine (4 µg bolus, then 0.05 µg/kg/min infusion) N=13 patients (cross-over design)	Both treatments decreased heart rate and cardiac output. PE had no effect on stroke volume. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Dyer et al. 2009 South Africa	20 women Mean 27.1 ± 3.7 years	Spinal Elective Cesarean delivery Substudy of 2.5 IU oxytocin applied after delivery w/wo PE N=10	80 µg bolus every 60 s for MAP < 80% baseline Mean 166.7 µg (80-240 µg) predelivery Mean 266 µg (80-800 µg) post-delivery	Ephedrine (10 mg) N=20 patients	Decrease in heart rate. Mean CO significantly lower at 150 s after PE injection compared to E. No safety events reported for PE in combination with oxytocin. No subject withdrawals or deaths.
Goertz et al. 1993a Germany	16 patients with no known CV disease (7M/9F) 31-41 years	General anesthesia Elective minor abdominal or orthopedic surgery	2 µg/kg IV bolus administered when MAP ≤ 80% of baseline	Norepinephrine comparator (0.1 µg/kg) N=16 patients (randomized crossover study to compare NE to PE)	PE caused a maximal decrease in fractional area change and mean velocity of fiber shortening at 30 seconds post-dose, returning to normal by 180 seconds post-dose. End systolic wall stress was almost doubled by PE. Despite cardiac changes, there were no deleterious effects reported for the patients. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Goertz et al. 1993b Germany	14 patients in coronary artery disease group (12M/2F) 10 patients in valvular aortic stenosis group (5M/5F) 49-78 years	General anesthesia Elective coronary artery bypass grafting or elective aortic valve replacement	PE (1 µg/kg bolus) or norepinephrine (0.5 µg/kg bolus) via central venous catheter in random order, the second substance being administered when arterial pressure and heart rate had returned to baseline	Norepinephrine (0.05 µg/kg) N=14 patients	Negative effects on left ventricular function in patients with coronary artery disease were present after PE administration, but not after norepinephrine. This same effect was not seen in aortic stenosis patients after either treatment. The effects appeared to be transient. PE caused a similar decrease in heart rate in both groups remaining at 180 s post-dose. No subject withdrawals or deaths.
Ishiyama et al. 2003 Japan	17 patients (7M/10F) Mean 63 ± 14 years	Combined general and epidural anesthesia Elective surgery	2 µg/kg IV (mean bolus dose of 112 µg)	Ephedrine (0.1 mg/kg) N=17 patients	Heart rate was decreased 2.5 minutes after administration. PE did not affect bispectral index compared to control values. Bispectral index is a measure of anesthesia depth. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Kee et al. 2007 China	74 women Age not specified	Spinal anesthesia Emergency Cesarean delivery	100 µg bolus IV whenever SBP < 100 mmHg	Ephedrine (10 mg) N=74 patients	Fetal acidosis not observed. Apgar scores for both groups said to be similar (values not given). No subject withdrawals or deaths.
Kwak et al. 2002 South Korea	14 patients with chronic pulmonary hypertension Mean age 56.8 ± 12.1 years M/F 3/11	General anesthesia Valvular heart surgery or repair of congenital heart defects	33.33 µg/min IV N=14 treated subjects	Norepinephrine (6.66 µg/min) N=10 patients	<u>At SAP ≥30% above baseline</u> Heart rate decreased significantly compared to baseline. Cardiac index did not change significantly from baseline. Systemic vascular resistance index, mean pulmonary arterial pressure, right atrial pressure and pulmonary vascular resistance index increased significantly compared to baseline. <u>At SAP ≥50% above baseline</u> Heart rate did not change significantly from baseline. Cardiac index decreased significantly compared to baseline. Systemic vascular resistance index, mean pulmonary arterial pressure, right atrial pressure and pulmonary vascular resistance index increased significantly compared to baseline.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
LaPorta et al. 1995	20 women Mean 31 ± 4 years	Spinal anesthesia Elective Cesarean delivery	Initial bolus dose of 80 µg IV 40 µg bolus injections as needed, given initially at an undisclosed level of hypotension to maintain systolic blood pressure above 100 mm Hg Mean dose: 364 ± 149 µg	Ephedrine 5 mg/mL N=20 patients	Maternal heart rate was decreased in the PE group, but not the E group. No Apgar scores < 7 at 1 or 5 minutes post-delivery. Fetal acidosis not observed. Maternal administration of PE was associated with lower neonatal catecholamine concentrations in the PE group compared to ephedrine group. No subject withdrawals or deaths.
Moran et al. 1991 United States	61 women Age not available	Spinal anesthesia Elective Cesarean delivery	80 µg initial IV bolus; 40 µg to 80 µg boluses during surgery to maintain maternal SBP above 100 mmHg Mean dose 335 ± 31 µg	Ephedrine 10 mg initial bolus; 5 mg/ml boluses as needed N=29 patients	Mean decrease in heart rate 26 bpm. No patient developed bradycardia. No adverse effects on the fetus or neonate were demonstrated by evaluation of acid-base status, Agpar scores, and Scanlon neurobehavioral exams. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Nygren et al. 2006 Sweden	10 patients (9M/1F) Mean 66 years (52-77)	Propofol sedation after uncomplicated coronary artery bypass surgery	0.5 ± 0.22 (0.21-0.94) µg/kg/min IV infusion 10-20 min titration period to achieve MAP 90 mm Hg, followed by 30-min study period. Each patient received sequentially and randomly both PE and norepinephrine in a cross-over study design	Norepinephrine (mean 0.52 µg/kg/min) N=10 patients	PE had no significant effects on heart rate, stroke volume or cardiac index. A 46% increase in systemic vascular resistance was observed, with slight increases in central venous pressure and pulmonary artery occlusion pressures observed. PE does not affect jejunal mucosal perfusion or gastric mucosal Pco_2 gradient in postcardiac surgery patients. PE promoted perfusion of splanchnic and hepatic vasculature. No subject withdrawals or deaths.
Pierce et al. 1994	26 women Mean 31.9 ± 4.2 yrs	Spinal anesthesia Elective Cesarean delivery	40 µg/mL in 1-2 mL bolus increments, as needed, to maintain systolic blood pressure above 100 mm Hg Mean predelivery dose 258.5 ± 138.2 µg (3.4 ± 1.8 µg/kg)	Ephedrine 5 mg/mL N=13 patients	Umbilical artery pH < 7.25 in one infant in PE group. No other safety findings reported. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Prakash et al. 2010 India	30 women Mean 24.1 ± 4.4 years	Spinal anesthesia Elective Cesarean delivery	1 ml bolus of 100 µg/ml IV, additional boluses administered if systolic pressure was ≤80% of baseline Mean total PE dose: 160 ± 60 µg	Ephedrine (1 ml bolus of 6 mg/ml) N=30 patients	5/30 (16.7%) women treated with PE developed bradycardia (heart rate <60 bpm). Mean heart rate decrease 20 ± 10 bpm from baseline. 3 women required atropine rescue due to heart rate < 45 beats/min. There was a higher likelihood of women developing bradycardia after PE administration than after ephedrine administration. This difference was not statistically significant. There were no instances of reactive hypertension observed. Heart rate > 100 bpm was reported for 6 patients. There were no instances of nausea or vomiting reported for the study. Fetal acidosis was not seen in any neonates. Apgar scores ≥8 at 1, 5 or 10 minutes post-delivery. Time to onset of rhythmic respiration <90 seconds for all groups. Neurobehavioral scores were similar for both groups. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Thomas et al. 1996 United Kingdom	19 women Mean age 30.0 years (95% CI:27.9-32.1)	Spinal anesthesia Elective Cesarean delivery	100 µg IV bolus dose when SAP decreased to ≤90% of baseline. Mean of 6 bolus injections used predelivery (1-10 range)	Ephedrine (5 mg) N=19 patients	Maternal heart rate decreased by mean 28.5% (24.2 to 32.9%) Atropine rescue required in 11/19 women with bradycardia. Cardiac output decreased by a mean of 8.9% (3.1 to 14.6%) No instances of fetal acidosis observed. Fetal heart rate decreased 4.3% (1.2 to 7.4%). All infants had Apgar scores ≥ 7 at 1 and 5 minutes. No subject withdrawals or deaths.
Uncontrolled Studies					
das Neves et al. 2010 Brazil	120 women (40 per group) Mean ages: Group 1: 30.78 ± 5.93 years Group 2: 29.8 ± 6.06 years Group 3: 29.3 ± 5.45 years	Spinal anesthesia Elective Cesarean delivery	Group 1: Prophylactic IV infusion of 0.15 µg/kg/min after spinal block Group 2: Prophylactic bolus of 50 µg after spinal block Group 3: Intervention bolus of 50 µg doses (as needed in case of hypotension)	None	Group 1: One patient experienced reactive hypertension (not further defined). Group 2: One patient experienced bradycardia (not further defined) Group 3: Higher incidence of nausea Fewer fetal side effects with PE. No subject withdrawals or deaths.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Uncontrolled Studies					
Dyer et al. 2008 South Africa	10 women with severe preeclampsia (8 treated before and 6 treated after delivery) 3 subjects received only PE during the study; the others also received ephedrine either before or after delivery. 24-40 years	Spinal anesthesia Urgent but not emergency Cesarean delivery	50 µg IV bolus PE was administered when MAP decreased by 20% from baseline and additional bolus doses administered every minute if needed. 100 µg IV PE was administered when MAP decreased by 30% from baseline and additional bolus doses administered every minute if needed.	None 5-10 mg ephedrine was given as an adjuvant if PE was ineffective (this occurred for 7 of the 10 subjects)	PE was associated with a significant decrease in HR. CO was not significantly changed from baseline, although a trend toward decrease from baseline was observed. Only two patients had symptoms during the surgical procedure; one had headache, and the other had blurred vision and epigastric pain. Apgar scores for all infants in study were ≥ 7 at 1 and 5 minutes. No cases of fetal acidosis were observed. Two patients reported symptoms of hypertension during surgical procedure. One had headache, one had blurred vision and epigastric pain. Dose combinations received by these patients is not known. 2.5 U oxytocin applied 30 seconds after delivery. Vasopressor was not applied for up to 3 minutes after the oxytocin administration. This did not result in any safety report.

Citation	Phenylephrine-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Phenylephrine Safety Findings
Uncontrolled Studies					
George et al. 2010 Canada	45 women Mean 34 ± 5 years	Spinal anesthesia Elective Cesarean delivery	Initial bolus dose 100 µg IV, then up or down increments by 20 µg as needed to maintain BP within 20% of baseline	None	Two subjects required treatment for bradycardia after receiving PE boluses. One subject was a treatment failure at 140 µg with a heart rate of 55 bpm. The subject's arterial blood pressure returned to 20% of baseline after atropine with no subsequent hypertension. The second subject was a treatment success at 160 µg PE and received glycopyrrolate for a heart rate of 49 bpm without hypotension. There was no instance of reactive hypertension when PE was administered alone or after rescue dose of glycopyrrolate was applied. No subject withdrawals or deaths.
Schwinn and Reves 1989	18 patients (gender not specified) Mean 63.2 ± 5.6 years	General anesthesia Elective coronary artery bypass graft surgery	50, 100, 150 or 200 µg IV bolus doses PE doses were randomized and applied sequentially to patients, 10 min after previous dose.	None	No ischemic events were associated with administration of IV PE. Significant decreases in heart rate were observed following 50 and 100 µg doses, but not after the 150 and 200 µg doses. This was not classified as bradycardia. Decreased cardiac output was also observed, with a trend toward dose response, although levels did not reach statistical significance. No subject withdrawals or deaths.

Source: Applicant's submission ISS (pp. 33-34)

Table 31 Literature to Support the Safety (b) (4)

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Placebo-controlled Studies					
Allen et al. 2010 United States	81 women Age not specified	Elective Cesarean delivery Spinal anesthesia	25, 50, 75 or 100 µg/min IV Prophylactic, fixed rate continuous infusion begun immediately after spinal anesthesia and continued until after delivery 100 µg bolus injected as needed to maintain maternal SBP N=81 treated subjects	Placebo N=20 patients	Three patients experienced AEs. All resolved spontaneously PE 100: 1 headache, 1 neck pain both seen after glycopyrrolate administration for the treatment of bradycardia. PE 50: Ventricular bigeminy not associated with hemodynamic instability Higher PE doses were associated with significantly higher incidence of predelivery hypertension and hypertensive episodes compared with placebo. PE no effects on Apgar scores at 1 and 5 minutes post-delivery. No fetal acidosis observed. Infusions permanently stopped in 15 pts in the PE 100 group due to reactive hypertension. Bradycardia (hr < 50 bpm) seen in 16 pts. 0.4 mg glycopyrrolate administered to 3 pts in PE25, 6 pts in PE 75 and 7 pts in PE 100 groups, but only 1 pt in placebo group. There were no deaths, events identified as serious, or withdrawals due to adverse events.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Placebo-controlled Studies					
El-Tahan 2011 Saudi Arabia	30 patients (22M/8F) Median 37.4 years (7.6)	Elective valve surgery General anesthesia	1.5 µg/kg IV prophylactic, single-dose infusion 1 min before induction of anesthesia	Placebo N=30 patients Ephedrine (either 0.07, 0.1, or 0.15 mg/kg) N=90 patients	A decrease in cardiac output, cardiac index, left ventricular stroke work index and stroke volume were seen for 20 minutes. PE was associated with an increase in ischemic episodes. Cardiac troponin I blood concentrations were not different from placebo for up to 48 h post-surgery A higher incidence of nitroglycerine rescues were seen in the PE group. PE had no effects on time to extubation, ICU length of stay, hospital length of stay or 30 day mortality rate. There were no deaths, events identified as serious, or withdrawals due to adverse events.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Placebo-controlled Studies					
El-Tahan 2011 Saudi Arabia	30 patients (22M/8F) Median 37.4 years (7.6)	Elective valve surgery General anesthesia	1.5 µg/kg IV prophylactic, single-dose infusion 1 min before induction of anesthesia	Placebo N=30 patients Ephedrine (either 0.07, 0.1, or 0.15 mg/kg) N=90 patients	A decrease in cardiac output, cardiac index, left ventricular stroke work index and stroke volume were seen for 20 minutes. PE was associated with an increase in ischemic episodes. Cardiac troponin I blood concentrations were not different from placebo for up to 48 h post-surgery A higher incidence of nitroglycerine rescues were seen in the PE group. PE had no effects on time to extubation, ICU length of stay, hospital length of stay or 30 day mortality rate. There were no deaths, events identified as serious, or withdrawals due to adverse events.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Placebo-controlled Studies					
Imran et al. 2007 Pakistan	89 patients (49M/40F) Mean age: 50 µg -- 32.39 ± 8.15 years 100 µg -- 35.69 ± 10.51 years	Elective surgery requiring laryngeal mask airway General anesthesia	Prophylactic, single-dose bolus of 50 or 100 µg PE mixed with 2.5 mg/kg propofol	Placebo (propofol + saline) N=43 patients	A transient dose dependent decrease in heart rate was observed. Maximal decrease seen at 2 minutes after administration. 50 µg dose resulted in maximum 38% decrease from baseline and minimum heart rate of 52 beats/min 100 µg dose resulted in maximum 50% decrease from baseline and minimum heart rate of 45 beats/min. There were no deaths, events identified as serious, or withdrawals due to adverse events.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Placebo-controlled Studies					
Langesaeter et al. 2008 Norway	40 women Mean 34± 1 years	Prospective, randomized, double-blind placebo controlled Caesarean delivery Spinal anesthesia	Prophylactic 0.25 µg/kg/min IV infusion delivered concomitantly with either 7 or 10 mg spinal bupivacaine for 20 minutes at beginning of anesthesia; 30 µg bolus injections then administered as needed N=60 treated subjects	Placebo N=40 patients	PE caused a decrease in CO and HR compared to placebo. Apgar scores were not affected by PE administration. Fetal acidosis not observed, although umbilical artery excess base was decreased in PE group compared to placebo. Little to moderate pruritis reported for 59 (73.8%), and severe pruritis for 9 (11.3%) of study participants. Treatment group allocation was not known. There were no deaths, events identified as serious, or withdrawals due to adverse events
Adequate and Well-Controlled Studies – Comparator Control					
Bjornestad et al. 2009 Norway	20 women Age not specified	Epidural anesthesia Elective Cesarean delivery	3 prophylactic 50 µg IV bolus doses administered just after anesthesia induction, 5 min post-induction, and at 10 min post-induction	Leg wrapping (no treatment comparator) N=20 patients	No instances of bradycardia (hr < 60 bpm) or hypertension were observed. No fetal acidosis was observed. All neonates had Apgar scores > 7 at 1 and 5 minutes post-delivery. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Hall et al. 1994 United Kingdom	10 women Mean 29.5 years (22-36)	Spinal anesthesia Elective Cesarean delivery	20 µg initial bolus followed by 10 µg/min, IV, then 20 µg bolus if hypotension occurred Total amount PE administered = 490 (300-680) µg.	Ephedrine (1, 2 mg/min, then 6 mg bolus if hypotension occurred) N=19 patients	Two subjects who received PE developed bradycardia (hr < 40 bpm). Fetal acidosis not observed. All Apgar scores ≥ 7 at 1 min and ≥ 9 at 5 min post-delivery. No subject withdrawals or deaths.
Kee et al. 2008 China	24 women treated with PE only Mean 32 ± 4 years	Spinal anesthesia Elective Cesarean delivery	0, 25, 50, 75, 100 µg/ml IV, in various combination with ephedrine Infusion rate variable Total median dose of PE for 100% PE group =890 (650-1085) µg.	Ephedrine (0, 2, 4, 6, 8 mg/ml) in combination with PE (inversely proportional) N=98 patients	No nausea or vomiting was reported for the PE group. Hypertension affected 12 patients (50%) of the PE only group. The maximum systolic blood pressure was 137 (132-147) mm Hg. Three (13%) subjects in the PE group experienced bradycardia. Minimum heart rate was 59 (53-67bpm). No instances of fetal acidosis were observed. Apgar scores all ≥ 7 at 1 min and ≥ 9 at 5 min post-delivery. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Mohta et al. 2010 India	30 women Mean 25 ± 3.5 years	Spinal anesthesia Elective Cesarean delivery	Prophylactic IV infusion of 50 µg/min started immediately after induction of anesthesia; 100 µg bolus doses applied as needed if hypotension occurred	Mephentermine (600 µg/min, 1.2 mg bolus as needed) N=30 patients	Among the PE group, 7 subjects developed bradycardia. 8 patients developed reactive hypertension, 2 of which were attributed to atropine. One complained of headache while the other had vomiting and ventricular ectopic beats. PE was stopped for these two patients. Apgar scores, umbilical blood gases and base deficit were all within normal ranges. No fetal acidosis observed. No subject withdrawals or deaths.
Pinto et al. 2008 Sri Lanka	30 women Mean 30.9 years	Spinal anesthesia Elective Cesarean delivery	33-67 µg/min (calculated), titrated to maintain baseline pressure until delivery	Ephedrine 5 mg boluses as needed N=30 patients	10% of subjects complained of headache, none experienced nausea or vomiting. 10% of neonates in PE group had Apgar scores < 5, with all ≥5 by 5 minutes post-delivery. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Sharrock et al. 1991 United States	9 patients (1M/8F) Mean 71.9 years (68-77)	Lumbar extradural anesthesia Total hip replacement surgery	Mean 10.6 ± 6.2 µg/min IV, doses varied to maintain mean arterial blood pressure within the desired range 50-60 mm Hg	Adrenaline (mean 2.6 µg/min) N=6 patients	PE and adrenaline had similar effects on MAP, but PE caused a decrease in CO and HR compared to adrenaline. PE caused higher and prolonged exposure to bupivacaine compared to adrenaline. No subject withdrawals or deaths.
Van Elsen et al. 2009 Belgium	49 women Age, weight, ASA status and race not specified	Spinal anesthesia Cesarean delivery	Prophylactic IV infusion of 20 µg/mL/min after induction of anesthesia If MAP was <80% baseline or <70 mmHg, an IV bolus of 100 µg PE was given.	Ephedrine (infusion of 1 mg/mL/min, 5 mg bolus as needed) N=48 patients	Duration of surgery and anesthesia, maternal saturation, blood loss, side effects, use of rescue medication, Apgar scores and umbilical blood gases were equal in PE and ephedrine (E) groups. Heart rate was higher in the E group than in the P group at 14, 16, 18, 20, 22, 24, 32, 36 minutes after spinal injection, but no difference was seen in the need to treat bradycardia with atropine.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Adequate and Well-Controlled Studies – Comparator Control					
Yoon et al. 2012 Korea	60 women Group P Mean 33 ± 3 years Mean 73 ± 7 kg Group PG Mean 34 ± 4 years Mean 70 ± 8 kg ASA status and race not specified	Spinal anesthesia Elective Cesarean delivery	After induction of anesthesia, PE was infused at 50 µg/min for 15 min, at which time PE infusion rate was determined within 80% of baseline SBP maintenance. If SBP fell to <80% baseline, 100 µg PE bolus or 10 mg ephedrine bolus was given depending on HR. Total PE dose was 552 ± 118 µg for Group P and 501 ± 154 µg for Group PG.	PE plus glycopyrrolate (0.2 mg)	No significant differences in stroke volume index in either group compared to baseline Heart rate and cardiac index were decreased significantly in Group P from baseline and from Group PG from eight minutes forward. There was no significant difference from baseline in Group PG. Incidence of bradycardia: 2 patients (Group P) Apgar scores at 1 min (median (range)) Group P: 8 (7-9) Group PG: 8 (6-9) Apgar scores at 5 min Group P: 9 (8-10) Group PG: 9 (8-10)

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
Ansari et al. 2011 United Arab Emirates	117 women Group 50 Mean 32.7 ± 4.6 years Mean 74.0 ± 9.1 kg Group 100 Mean 32.8 ± 5.3 years Mean 75.5 ± 9.9 kg ASA status I, II Race not specified	Spinal anesthesia Elective Cesarean delivery	After induction of anesthesia, rapid crytalloid co-loading and infusion of PE (either 50 µg/min or 100 µg/min) were initiated. PE infusion continued for 3 min and stopped if SBP was >120% of baseline; if SBP was between 80-100% of baseline, PE continued until delivery. A rescue dose of PE (50 µg) was administered if SBP decreased to <80 of baseline. Mean PE dose was 549.6 ± 211.3 µg in Group 50 and 913.5 ± 361.4 in Group 100.	None	1 patient in Group 50 (1.8%) 11 patients in Group 100 (17.4%) developed bradycardia (HR < 50 bpm) (p=0.005). 3 patients in Group 50 (5.5%) and 1 patient in Group 100 (1.5%) experienced nausea and vomiting (p=0.33). 7 patients in Group 50 (12.9%) and 1 patient in Group 100 (1.5%) required rescue doses of PE (p=0.023). None of the neonates had an umbilical artery pH <7.2. Apgar scores at 1 minute were ≥7 and at 5 minutes were ≥9. All umbilical arterial and venous blood gas values were not different between neonates in both groups except the umbilical arterial PCO_2 that was significantly higher in neonates in Group 100 (52.5 vs. 55.4, p<0.05).

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
Cooper et al. 2012 United Kingdom	100 healthy women Median 30 yrs (26-34) Median 70 kg (62-78) ASA status I, II Race not specified	Spinal anesthesia Elective Cesarean delivery	After induction of anesthesia, an infusion of PE was started at 67 µg/min (max allowable rate); the infusion rate was altered with the aim of keeping SAP ≥80% but ≤120% of baseline. If SBP declined to <80% of baseline, a 100 µg bolus of PE was given.	None	During anesthesia, heart rate decreased from raised anesthetic room values to significantly below baseline. Bradycardia (HR <60 bpm) associated with hypotension occurred in 2 patients. 13 patients developed one episode of nausea each: 11 mild, 1 moderate, 1 severe.
das Neves et al. 2010 Brazil	120 women (40 per group) Mean ages: Group 1: 30.78 ± 5.93 years Group 2: 29.8 ± 6.06 years Group 3: 29.3 ± 5.45 years	Spinal anesthesia Elective Cesarean delivery	Group 1: Prophylactic IV infusion of 0.15 µg/kg/min after spinal block Group 2: Prophylactic bolus of 50 µg after spinal block Group 3: Intervention bolus of 50 µg doses (as needed in case of hypotension)	None	Group 1: One patient experienced reactive hypertension. Group 2: One patient experienced bradycardia Group 3: Higher incidence of nausea Fewer fetal side effects with PE. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
de Souza et al. 2011 Brazil	60 women <u>Group 12</u> Mean 31 ± 6.2 years Mean 73.3 ± 10 kg <u>Group 8</u> Mean 31.1 ± 5.8 years Mean 74.5 ± 11.8 kg ASA status I, II Race not specified	Spinal anesthesia Elective Cesarean delivery	After induction of anesthesia with either 8 or 12 mg hyperbaric bupivacaine, PE was infused at 100 µg/min; the rate was adjusted to maintain blood pressure at baseline levels. If SBP fell by more than 10% of baseline, a bolus of 50 µg PE was given. Total mass of PE was 1,024.3 ± 277.4 µg for Group 12 and 794.4 ± 281.1 µg for Group 8.	None	Nine patients developed bradycardia; 4 in the 12 mg group and 5 in the 8 mg group. Maternal adverse events (number of episodes): 1 nausea (Group 12), 0 vomiting, 0 pain, 1 dyspnea (Group 8), 10 tremors (4 Group 12, 6 Group 8) 1 neonate had an Apgar score of 3 at 1 minute; all others were above 7. All scores were above 7 at 5 minutes.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
Kee et al. 2004 China	74 women 18-43 years	Spinal anesthesia Elective Cesarean delivery	100 µg/min, IV for 2 min, then 100 µg/min each min as needed to maintain SBP ≤ 100%, 90% or 80% of baseline. Total median dose of PE: 100% = 1520 (1250-2130) µg 90% = 1070 (890-1360) µg 80% = 790 (590-950) µg	None	Maternal HR was comparatively low in most patients. One patient each in the 80% and 90% groups required atropine intervention due to bradycardia accompanied by hypertension. Hypertensive events were comparable in the three PE dosing groups, ranging from 16-24% incidence. Nausea and/or vomiting was reduced as patient's blood pressure was maintained nearer to baseline. Fetal acidosis was not observed in any of the PE dose groups. One infant in PE 100 group had an Apgar score < 7 at 1 minute. All infants had Apgar scores >9 by 5 minutes post-delivery. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
Stewart et al. 2010 United Kingdom	75 women Mean ages: 25 µg/min: 32 ± 5 years 50 µg/min: 33 ± 6 years 100 µg/min: 34 ± 5 years	Combined spinal/ epidural anesthesia Elective Cesarean delivery	25, 50 or 100 µg/min, to maintain BP; 100 µg bolus as needed Mean PE doses: 25 µg/min = 779 ±247 µg 50 µg/min = 1380 ± 515µg 100 µg/min = 2300 ± 847 µg	None	There were significant time and dose-dependent reductions in HR and CO with PE, such that HR and CO were seen to decrease with time in each group, and also with increasing concentrations of PE. Stroke volume remained stable throughout. Two subjects in the 25 µg group required glycopyrrolate intervention for bradycardia. There were no significant differences between dose groups with respect to umbilical artery pH or base excess, and Apgar scores were noted not to be different. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Uncontrolled Studies					
Tanaka et al. 2009 Canada	50 women Mean 34.5 ± 3.8 years	Spinal anesthesia Elective Cesarean delivery	40-120 µg IV bolus, one prophylactic then as needed to maintain BP 40 µg initial bolus then adjusted by 10 µg increments or decrements	None	Hypertension was seen in 14 patients at different dose levels. All incidents of hypertension were observed with the first dose of PE applied immediately after anesthesia. No patient experienced more than one episode of hypertension. No headache, chest pain or shortness of breath were reported. Bradycardia (hr < 50 bpm) was not seen in the study. Nausea was seen in 11 patients, 4 cases were not accompanied by hypotension. Vomiting was not seen in any patient. Umbilical artery pH <7.2 in two patients who did not respond to phenylephrine pressor therapy. Apgar scores for all infants was > 7 at 1 and 5 minutes post-delivery. No subject withdrawals or deaths.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Miscellaneous Supportive Studies					
Ayorinde et al. 2001 United Kingdom	54 women (27 per group) Mean ages: 4 mg: 30.1 years (18-41) 2mg: 31.3 years (22-38)	Spinal anesthesia Elective Caesarean delivery	Prophylactic, single-dose, 2 or 4 mg IM injection	Placebo N=27 patients Ephedrine (prophylactic single-dose 4 mg IM injection) N=27 patients	No reported safety findings. None of vasopressor therapy regimes had any impact on fetus in terms of umbilical cord venous blood pH and Apgar scores. There were no deaths, events identified as serious, or withdrawals due to adverse events.
Cheng et al. 1999 China	60 patients (20 per group) (48M/12F) Mean ages 50 µg: 64 ± 3 100 µg: 63 ± 2 200 µg: 68 ± 3	Epidural anesthesia Herniorrhaphy	Prophylactic, single-dose PE injection (50, 100 or 200 µg); injected concomitantly with alkalized lidocaine directly to the epidural space	Placebo N=20 patients	1 patient experienced severe hypertension and mental confusion with 200 µg PE due to direct absorption of the 200-mg PE-alkalinized lidocaine mixture through a lacerated epidural vessel. 200 µg PE caused HR to be closer to baseline than lower doses of PE. There were no deaths, events identified as serious, or withdrawals due to adverse events.
Cooper et al. 2010 United Kingdom	148 women 29 years (22-33) Retrospective case review	Spinal anesthesia High-risk Cesarean delivery	33 µg/min IV infusion following spinal injection, titrated to maintain blood pressure at baseline. 100-µg bolus infusions were administered for hypotension.	Ephedrine 6 mg boluses as needed N=122 patients No vasopressor N=115 patients	No adverse effects on the fetus or neonate were demonstrated vs. no vasopressor by evaluation of acid-base status, Agpar scores.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Miscellaneous Supportive Studies					
Guillon et al. 2010 France	30 women Mean 33 ± 5 years	Spinal anesthesia Elective Cesarean delivery	2.5 mg/hr IV prophylactic infusion, adjusted to maintain BP within desired range (10% of preoperative)	Ephedrine 195 mg/hr N=20 patients	Neither PE nor ephedrine modified QTc. No arrhythmias were observed with continuous ECG monitoring No subject withdrawals or deaths.
Mercier et al. 2001 France	19 women Mean 34 ± 5 years	Spinal anesthesia Elective Cesarean delivery	10 µg/min PE mixed with 2 mg/min ephedrine, IV	Ephedrine (2 mg alone) N=20 patients	PE added to an infusion of ephedrine halved the incidence of hypotension and increased umbilical cord pH. No subject withdrawals or deaths.
Nishikawa et al. 2002 Japan	60 subjects (15 per group; 30M/30F) Mean ages: Normotensive 3 mg: 72 ± 9 1.5 mg: 74 ± 7 Hypertensive 3 mg: 74 ± 7 1.5 mg: 75 ± 5	Spinal anesthesia Hip fracture repair	Prophylactic, single-dose, 1.5 mg or 3 mg IM injection	Placebo N=30 patients (15 normotensive, 15 hypertensive)	No patients developed bradycardia. One patient in the normotensive PE (3 mg) group and two patients in the hypertensive PE (3 mg) group required nicardipine because of hypertension after the study medication. There were no deaths, events identified as serious, or withdrawals due to adverse events.

Citation	PE-Treated Subjects	Type of Anesthesia/ Surgical Procedure	Phenylephrine Dose, Administration	Comparator Arm	Safety Findings
Miscellaneous Supportive Studies					
Sakura et al. 2001 Japan	100 Adolescents: 24M/16F; age 13-16 years Adults: 45M/15F; age 25-74 years	Spinal anesthesia Lower limb arthroscopy	Intraspinal PE 0.125%, concomitant with lower or higher glucose solutions, administered to a variety of lumbar interspace sites	None	Bradycardia: maximum percent decrease in systolic blood pressure 9.0-9.7% There were no safety findings related to subject age. No subject withdrawals or deaths.

Source: Applicant's submission ISS (pp. 89-105)

9.1 Literature Review/References

Synopses of the published clinical studies that were used as a basis for the efficacy are summarized below.

9.1.1 Treatment of hypotension during anesthesia

9.1.1.1 Active controlled studies:

Obstetric surgery under neuraxial anesthesia:
D. H. Moran 1991
In this randomized, double-blind trial, phenylephrine and ephedrine were compared in the prevention of maternal hypotension following spinal anesthesia for elective cesarean delivery.

Sixty healthy patients electively scheduled for cesarean delivery under spinal anesthesia. Patients were randomly assigned to receive either ephedrine (n = 29) in 10 mg intravenous (IV) bolus injections or phenylephrine (n = 31) in 80 mcg IV bolus injections to maintain systolic blood pressure (SB P) above 100 mmHg.

Results: Maternal venous, umbilical artery, and umbilical vein blood gases were measured, and neonatal Apgar scores and Early Neonatal Neurobehavior Scale scores were assessed. In the ephedrine group, umbilical artery PH was 7.28 k 0.01 (mean + SEM), umbilical artery partial pressure of carbon dioxide {PCO,) was 56.6 5 1.4 mmHg, and umbilical artery base deficit was 2.2 -t 0.04 meq. In the phenylephrine group, umbilical artery PH was 7.32 k 0.01, umbilical artery PCO, was 52.1 k 1.3 torr, and umbilical artery base deficit was 0.38 + 0.35 meq. There were significant differences between the groups in mean umbilical artery PH, PCO, and base deficit, although all values obtained were within normal limits. There were no significant differences between the groups in the remaining acid-base values, neonatal Apgar scores, Early Neonatal Neurobehavior Scale scores, or frequency of maternal nausea and vomiting.

Conclusions: Phenylephrine is as effective as ephedrine in the treatment of maternal hypotension, and when used in small incremental bolus injections, it appears to have no adverse neonatal effects in healthy, non-laboring parturients.

Discussion: This study suggests that both phenylephrine and ephedrine could maintain SBP over 100 mmHg, the study focused on neonatal outcomes.

D. G. Thomas 1996
In this randomized, double-blind study, PE and ephedrine in 38 women undergoing elective Cesarean delivery under spinal anesthesia were compared.

After induction of anesthesia, arterial pressure was measured at 1 min intervals. Whenever SAP decreased to < 90% of baseline, 1 mL of study agent (5 mg of ephedrine or 100 mcg of PE) was given.

Results: Maternal BP and CO changes were similar in both groups, but the mean maximum percentage change in maternal HR was larger in the PE group as the table and figure below:

Table 2 Maternal haemodynamic data. Figures are mean (95 % confidence intervals) or median (range)*. SAP = systolic arterial pressure)

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Conclusion: The study supports the use of PE for maintenance of maternal arterial pressure during spinal anaesthesia for elective Caesarean section.

Discussion: This study suggests that both phenylephrine and ephedrine maintain maternal BP similarly, but bradycardia is profound in phenylephrine group.

S. Prakash 2010
In this randomised double-blind study, maternal haemodynamic changes and neonatal well-being following bolus administration of ephedrine and phenylephrine were compared in 60 term parturients undergoing elective caesarean delivery under spinal anaesthesia.

Women received boluses of either ephedrine 6 mg (group E; n=30) or phenylephrine 100 mcg (group P; n=30) whenever maternal systolic pressure was < 80% of baseline.

Results: Changes in systolic pressure were comparable in the two groups. There were no differences in the incidence of bradycardia (group E: 0% vs. group P: 16.7%; P>0.05), nausea (group E: 13% vs. group: P 0; P>0.05) and vomiting (group E: 3.3% vs. group P: 0; P>0.05) as in the table and figures below. Umbilical artery (UA) pH (group E: 7.29 ± 0.04 vs. group P: 7.32 ± 0.04; P=0.01) and venous pH (group E: 7.34 ± 0.04 vs. group P: 7.38 ± 0.05; P=0.002) were significantly greater in group P than in group E. UA base excess was significantly less in group E (-2.83 ± 0.94 mEq/L) than in group P (-1.61 ± 1.04 mEq/L; P<0.001). Apgar scores at 1, 5 and 10min and neurobehavioural scores at 2-4 h, 24 h and 48 h were similar in the two groups (P>0.05).

Conclusions: Phenylephrine 100 mcg and ephedrine 6 mg had similar efficacy in the treatment of maternal hypotension during spinal anaesthesia for elective caesarean delivery. Neonates in group P had significantly higher umbilical arterial pH and base excess values than those in group E, which is consistent with other studies.

Discussion: This study suggests that both phenylephrine and ephedrine maintain maternal BP similarly, but bradycardia is present in phenylephrine group.

R. A. Dyer, 2009
In this randomized, double-blind study, effects of bolus phenylephrine and ephedrine on maternal cardiac output (CO) were compared. Forty-three patients were randomized to receive 80 mcg of phenylephrine or 10 mg of ephedrine. Both pulse wave form analysis and transthoracic bioimpedance changes were used to estimate stroke volume in each patient. Hemodynamic responses to spinal anesthesia and oxytocin were also recorded. A subgroup of 20 patients was randomized to receive oxytocin compared with oxytocin plus 80 mcg of phenylephrine after delivery.

Results: Mean CO and maximum absolute response in CO were significantly lower during the 150 s after phenylephrine administration than after ephedrine as the figure below. CO changes correlated with heart rate changes. Coadministration of phenylephrine obtunded oxytocin-induced decreases in systemic vascular resistance and increases in heart rate and CO. Trends in CO change were similar using either monitor.

Conclusions: Bolus phenylephrine reduced maternal CO, and decreased CO when compared with ephedrine during elective spinal anesthesia for Cesarean delivery. CO changes correlated with heart rate changes after vasopressor administration, emphasizing the importance of heart rate as a surrogate indicator of CO. Coadministered phenylephrine obtunded hemodynamic responses to oxytocin.

A. Alahuhta 1992
In this randomized,double-blind study, comparison of PE (n=8) and ephedrine (n=9) in elective Cesarean delivery under spinal anesthesia was conducted.

PE of (b) (4) 1 mL IV bolus was given, followed by continuous infusion of 10 mL/hour (1 mL = 100 mcg). If SAP fell by >10mm Hg from baseline, bolus injections to supplement infusion was allowed. Ephedrine was administered as with PE; 1 mL = 5 mg ephedrine).

Results: Mean SAP at base, initiation of PE, and lowest value were 125+/- 11.7, 109+/- 13.5 and 115+/-17 respectively as the table below:

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Conclusion: PE administered in this manner was effective at correcting maternal hypotension during spinal anesthesia.

Non-obstetric studies under general anesthesia
A. W. Goertz 1993a
This is a randomized, unblinded study of 16 patients undergoing elective minor abdominal or orthopedic surgery under general anesthesia with thiopental receive PE

and norepinephrine in isoflurane induced hypotension. Study conducted after induction of anesthesia but prior to surgical procedure.

After MAP ≤ 80% of baseline, subjects received an IV bolus of PE (2 mcg/kg) or norepinephrine (0.1 mcg/kg) in random order. After receiving an initial bolus of one drug, patients received a bolus of the other drug after BP and HR returned to baseline levels but not earlier than 5 min after the first injection.

Results: Hemodynamic data are presented in table below. All patients showed increases in MAP which peaked between 30 and 50 seconds and between 22 to 45 seconds after bolus injection of PHE and NE, respectively.

Conclusion: Both agents effectively restored arterial blood pressure. PE, iven as intravenous bolus to patients under isoflurane hypotension, causes a transient impairment of left ventricular systolic performance.

Discussion: It is study of using transesophageal echocardiogram to exam the left ventricular function.

A. W. Goertz 1993b

This is a randomized, unblinded study of patients undergo elective coronary artery bypass grafting (n=20) or elective aortic valve replacement (n=18) under general anesthesia. When MAP was >10% less than lowest reading in previous 24 hours, 1 mcg/kg bolus of PE was administered via central venous catheter. The comparator is bolus injection of norepinephrine (0.05 mcg/kg), administered in same manner.

Results: Both agents effectively restored arterial pressure in both groups as the table below.

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Conclusion: PE bolus administration is an effective vasopressor in CAD and AS patients. PE also causes a transient impairment of LV global function.

Discussion: It is another study of using transesophageal echocardiogram to exam the left ventricular function in different population.

A. Nygren 2006
In a randomized, unblinded crossover study, ten patients were studied during propofol sedation and mechanical ventilation after uncomplicated coronary artery bypass surgery. Each patient received randomly and sequentially norepinephrine (0.052 mcg/kg/min) and phenylephrine (0.50 mcg/kg/min) to increase mean arterial blood pressure by 30%.

Results: Both drugs induced a 40–46% increase in systemic vascular resistance with no change in cardiac index. Neither jejunal mucosal perfusion, jejunal mucosal hematocrit, red blood cell velocity, nor gastric-arterial PCO2 gradient was affected by any of the vasopressors. Splanchnic oxygen extraction increased from 38.2% to 43.1% ($p < .001$) with norepinephrine and from 39.3% to 47.5% ($p < .001$) with phenylephrine. This increase was significantly more pronounced with phenylephrine compared with norepinephrine ($p < .05$). Mixed venous-hepatic vein oxygen saturation gradient increased with both drugs ($p < .01$), and the increase was more pronounced with phenylephrine ($p < .05$). Splanchnic lactate extraction was not significantly affected by any of the vasopressors.

Conclusions: Phenylephrine induced a more pronounced global alpha 1-mediated splanchnic vasoconstriction compared with norepinephrine. Neither of the vasoconstrictors impaired perfusion of the gastrointestinal mucosa in postcardiac surgery patients. The lack of norepinephrine-induced, alpha 1-mediated impairment of gastrointestinal perfusion is not explained by alpha 2-mediated counteractive vasodilation but instead by possible mucosal autoregulatory escape.

Y. L. Kwak 2002
In this study the effect of phenylephrine and norepinephrine for the treatment of systemic hypotension were evaluated in 24 patients with chronic pulmonary hypertension. When systemic hypotension (systolic arterial pressure,100 mmHg) occurred following induction of anaesthesia, either phenylephrine (n=14) or norepinephrine (n=10) were infused in a random manner to raise the systolic blood pressure by 30% and 50% above baseline values.

Results: Norepinephrine decreased the ratio of pulmonary arterial pressure to systemic blood pressure without a change in cardiac index. However, phenylephrine did not increase arterial blood pressure by more than 30% from baseline in one-third of patients and decreased cardiac index without a significant decrease in ratio of pulmonary arterial pressure to systemic blood pressure. These vasoconstrictors showed different systemic and pulmonary haemodynamic effects in patients with chronic pulmonary hypertension as compared to acute pulmonary hypertension.

Conclusion: Norepinephrine was considered to be preferable to phenylephrine for the treatment of hypotension in patients with chronic pulmonary hypertension.

Non-obstetric studies under general anesthesia

R. F. Brooker 1997

In this randomized,double-blind cross-over study, a total of 14 patients undergoing elective surgery (5 orthopedic, 6 urologic, 2 gynecologic operations) under spinal anesthesia received PE and epinephrine.

After spinal anesthesia, when there was a 15% drop in SAP, treatment was initiated with the first vasopressor (bolus followed by infusion). After completion of the first treatment, here was a 10 min washout period, and then the second drug was given in the same manner.

When a 15% reduction in SAP occurred, treatment was initiated with a 40 mcg bolus of PE, followed by an infusion of PE (0.5 mcg/kg/min). If SBP did not increase with the initial infusion, repeat bolus doses could be given, or the infusion rate could be doubled. Epinephrine; initial bolus dose of 4 mcg, followed by infusion of 0.05 mcg/kg/min administered in the same manner.

Results: PE increased SBP from 120 ± 6 mm Hg to 144 ± 5 mm Hg ($p<0.001$), and restored MAP from 82 ± 4 mm Hg to 100 ± 4 mm Hg ($p<0.001$).

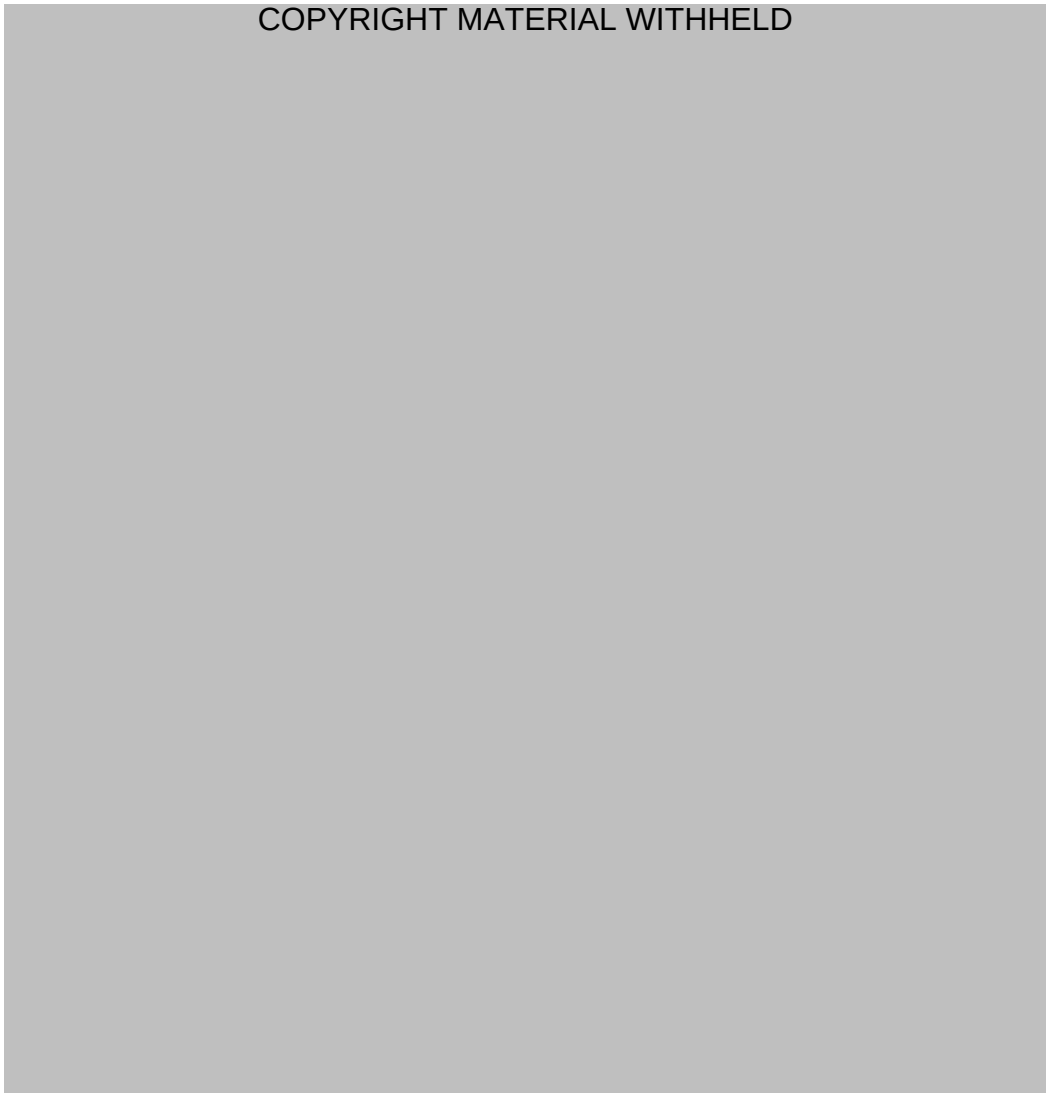
Conclusion: PE effectively restored SBP, MAP, and DBP after spinal anesthesia.

Non-obstetric study under combined general and neuraxia anesthesia

T. Ishiyama 2003

The effects of ephedrine versus phenylephrine on bispectral index (BIS) during combined general and epidural anesthesia was studied. After injection of ropivacaine through the epidural catheter, general anesthesia was induced with propofol and vecuronium, and was maintained with 0.75% sevoflurane. Approximately 10 min after the intubation, BIS was recorded as a baseline value. Patients with decreases in arterial blood pressure <30% of the preanesthetic values were defined as control group (n=9). Patients who had to be treated for larger decreases in arterial blood pressure were randomly assigned to receive ephedrine 0.1 mg/kg (n =17) or phenylephrine 2 mcg/kg (n =17). BIS values were recorded at 1-min intervals for 10 min.

Results: Mean blood pressure during BIS value acquisition was comparable among the three groups except baseline. Heart rate during BIS value acquisition was significantly faster in the ephedrine group than in the other groups as the figure below. BIS in the ephedrine group was significantly larger from 7 to 10 min than that in the control and phenylephrine groups. Seven patients in the ephedrine group had BIS >60, whereas no patient in the control and phenylephrine groups had BIS >60.



Conclusion: Ephedrine, but not phenylephrine, increased BIS during general anesthesia combined with epidural anesthesia.

9.1.1.2 Non active controlled studies

Obstetric studies:

R. B. George 2010

In this double-blind up-down study to estimate the 90% effective dose of IV PE, healthy no-laboring women undergoing a cesarean delivery were recruited.

All women received spinal anesthesia using hyperbaric bupivacaine 12 mg with fentanyl and morphine. Each subject received an IV crystalloid fluid bolus before and at the time of initiation of spinal anesthesia (preload and coload). An up-down sequential allocation method using the biased-coin design was used to estimate the 90% effective dose (ED90) of phenylephrine. The assigned phenylephrine dose was based on the response

of the preceding subject. If the systolic blood pressure (SBP) decreased 20% of baseline (i.e., SBP 20%) or to an SBP 90 mmHg, the assigned dose of phenylephrine was administered. If the SBP returned to within 20% of baseline or 90 mm Hg within 1 min, this was considered a success, otherwise it was a failure. The initial dose of phenylephrine was 100 mcg. The ED90 with 95% confidence intervals (CIs) was calculated using the maximum likelihood estimation and Firth logistic regression.

RESULTS: Forty-five of the enrolled subjects experienced spinal anesthesia induced hypotension and received a blinded dose of phenylephrine. Those subjects who developed hypotension received doses of phenylephrine between 80 and 180 mcg. No subjects experienced hypertension. Determined with the maximum likelihood estimation method, the ED90 of phenylephrine was 147 mcg (95% CI, 98–222 mcg). With Firth regression, the probability of a successful response at 150 mcg is 90.5% (95% CI, 66.0%–99.0%).

CONCLUSION: ED90 of phenylephrine required to treat spinal anesthesia-induced hypotension in cesarean delivery is approximately 150 mcg.

J. Neves 2010

In this randomized, double-blind study, one hundred and twenty gravidas undergoing elective cesarean sections under spinal block, randomly divided in three equal groups according to the regimen of phenylephrine administered, were included in this study. In Group 1, continuous infusion of phenylephrine, using an infusion pump at 0.15 mcg.kg-1.min-1 was administered after the spinal block. In Group 2, a single dose of (b) (4) phenylephrine 50 mcg was administered after the spinal block, and Group 3 received a single dose of phenylephrine 50 mcg in case of hypotension, which was defined as a drop in SBP and/or DBP of up to 20% of baseline levels. The incidence of hypotension, nausea, and vomiting as well as the Apgar score were evaluated.

Results: The incidence of hypotension was significantly greater in Group 3, affecting 85% of the gravidas. In Groups 1 and 2, hypotension was seen in 17.5% and 32.5% of the cases respectively ($p < 0.001$) as the table below. The incidence of nausea was much higher in Group 3 affecting 40% of the patients while in Groups 1 and 2 it was 10% and 15% respectively which was statistically significant.

Conclusions: According to the methodology used, this study showed that (b) (4) continuous infusion of phenylephrine initiated immediately after the spinal block for cesarean section is more effective in reducing the incidence of hypotension and maternal and fetal side effects.

R. A. Dyer, 2008

Hemodynamic responses to spinal anesthesia (SA) for cesarean delivery in patients with severe preeclampsia were studied by using a beat-by-beat monitor of cardiac output (CO) to characterize the response to SA. The hypothesis was that CO would decrease from baseline values by less than 20%.

Fifteen patients with severe preeclampsia consented to an observational study. The monitor employed used pulse wave form analysis to estimate nominal stroke volume. Calibration was by lithium dilution. CO and systemic vascular resistance were derived from the measured stroke volume, heart rate, and mean arterial pressure. In addition, the hemodynamic effects of phenylephrine, the response to delivery and oxytocin, and hemodynamics during recovery from SA were recorded. Hemodynamic values were averaged for defined time intervals before, during, and after SA.

Results: Cardiac output remained stable from induction of SA until the time of request for analgesia. Mean arterial pressure and systemic vascular resistance decreased significantly from the time of adoption of the supine position until the end of surgery. After oxytocin administration, systemic vascular resistance decreased and heart rate and CO increased. Phenylephrine, 50 mcg, increased mean arterial pressure to above target values and did not significantly change CO as the table below. At the time of recovery from SA, there were no clinically relevant changes from baseline hemodynamic values.

Table 5. Effects of Phenylephrine on Hemodynamic Parameters Using Data from All Doses of Phenylephrine (n = 20)

	Pre, Mean (SD)	Post, Mean (SD)	Estimated Change	99% CI
CO, l/min	6.3 (1.5)	5.8 (1.6)	−0.5	−1.1 to 0.2
SVR, dyn · s · cm^{-5}	1,155 (297)	1,507 (469)	352	59 to 645
MAP, mmHg	91 (13)	108 (15)	17	8 to 24
SV, ml/beat	75.9 (18.7)	78.7 (20.5)	2.8	−2.4 to 8.1
HR, beats/min	84.2 (15.1)	74.9 (10.8)	−9.3	−17.2 to −1.4

Heart rate (HR) decreased significantly, and mean arterial pressure (MAP) and systemic vascular resistance (SVR) increased significantly after phenylephrine administration.

CI = confidence interval; CO = cardiac output; pre = averaged values before phenylephrine; post = averaged values after phenylephrine; SV = stroke volume.

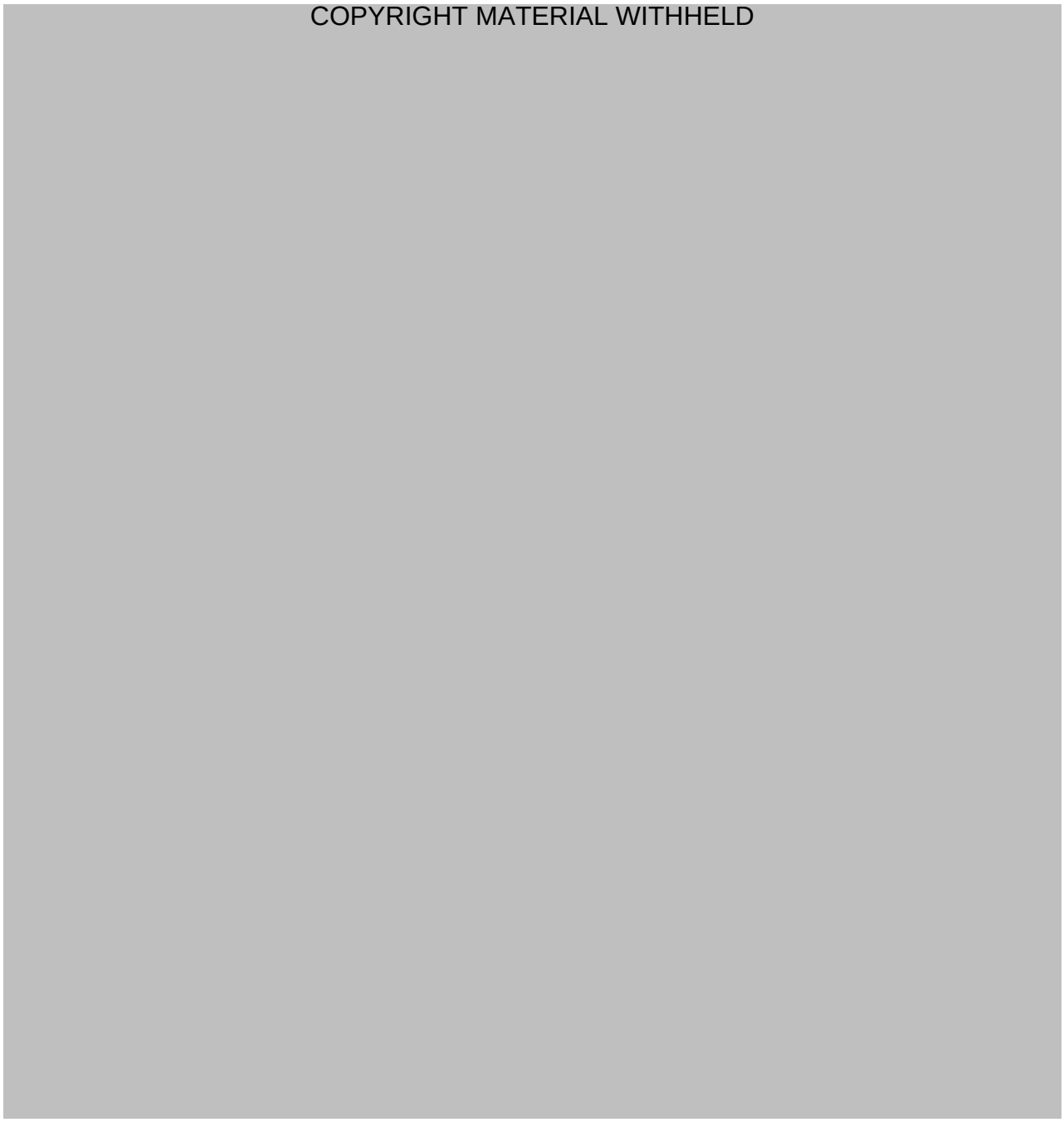
Conclusions: Spinal anesthesia in severe preeclampsia was associated with clinically insignificant changes in CO. Phenylephrine restored mean arterial pressure but did not increase maternal CO. Oxytocin caused transient marked hypotension, tachycardia, and increases in CO.

Non-obstetric studies

D. A. Schwinn and J. G. Reves 1989

Fifty randomized IV bolus doses of PE (50, 100,150, or 200 mcg) were given to 18 patients during anesthesia for elective coronary artery surgery. Esophageal Doppler techniques were used to continuously monitor cardiac output (CO); mean arterial pressure (MAP), CO, and calculated systemic vascular resistance (SVR) were recorded every 5 seconds for a total of 2 minutes.

Results: The hemodynamic changes as the table below for each of the four doses of PE (50,100, 150, 200 mcg) were maximal at about 42 seconds after the drug was given. They consisted of an increase in MAP; increase in SVR and a decrease in CO.



Conclusion: bolus IV PE in patients with myocardial disease increases MAP and SVR and simultaneously decreases CO; these peak hemodynamic events occur approximately 42 seconds after PE administration.

9.1.2 (b) (4) of hypotension during anesthesia

9.1.2.1 Placebo-controlled studies

Bolus

El-Tahan (2011)

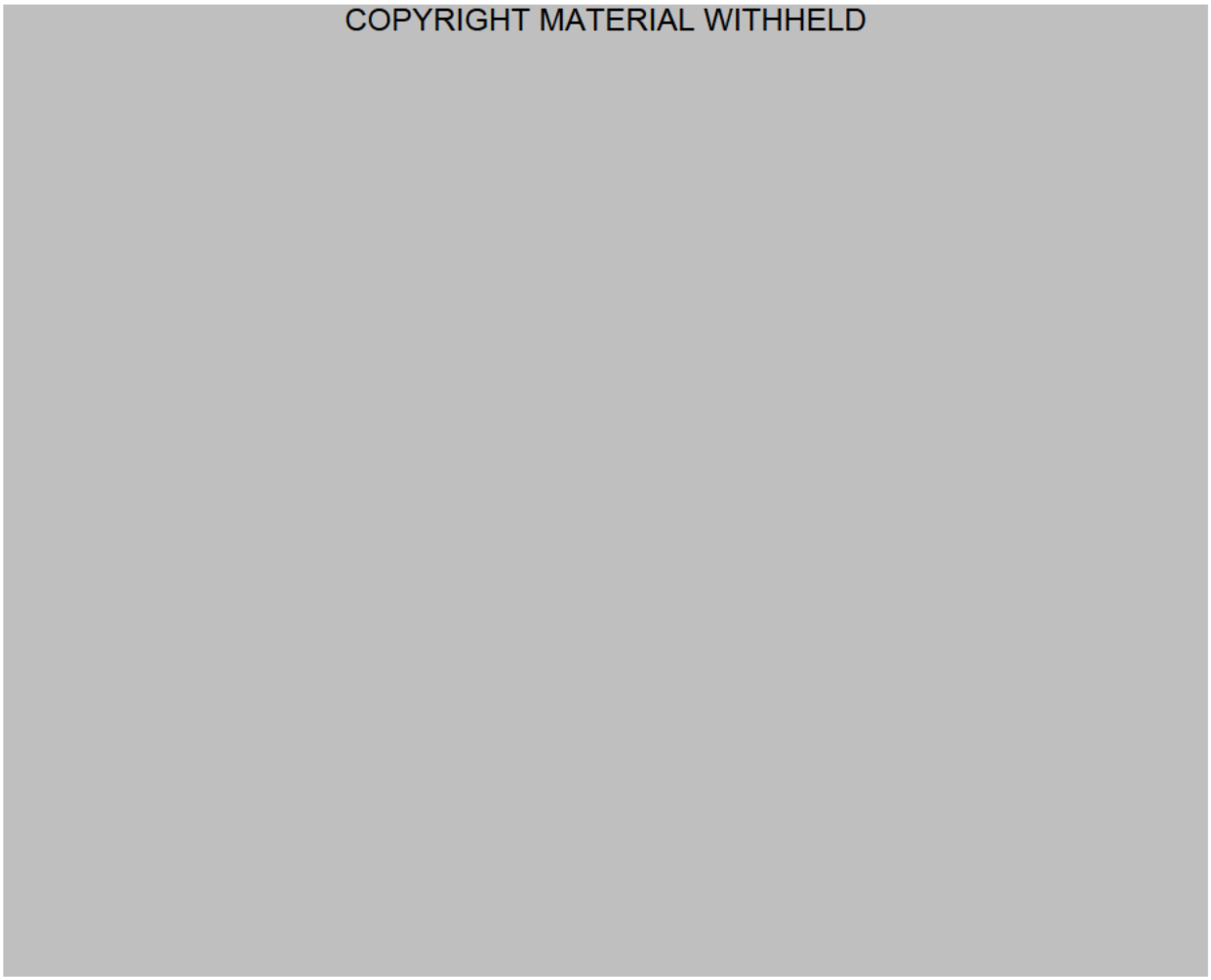
El-Tahan (2011) reported on a prospective, randomized, double-blind placebo controlled evaluation of several doses of ephedrine, with phenylephrine 1.5 mcg/kg as active comparator and saline as placebo control, (b) (4) hypotension associated with general anesthesia during elective surgery to replace or repair cardiac valves. One hundred fifty patients (30 per group) were administered single dose test drugs, each 0.1 mL/kg, administered over 1 minute, 1 minute before induction of propofol-fentanyl anesthesia. Hemodynamic measurements were made during the surgery, and rescue treatments (hydroxyethyl starch for hypotensive episodes) were given to maintain mean arterial pressure and heart rate within 20% of baseline values. Primary outcome variables included changes in mean arterial pressure, systemic vascular resistance and cardiac index, measured at baseline, following induction of anesthesia and up to 15 minutes after sternotomy. Other hemodynamic indices and the need for vasoactive drugs constituted secondary variables.

Efficacy evaluations showed that phenylephrine 1.5 mcg/kg produced hemodynamic effects similar to the lowest ephedrine dose, counteracting the hypotensive effects observed in the placebo group. Representative hemodynamic effects based on mean arterial pressure are demonstrated below in the figure.

MAP, SVRI, CI and SVI during Surgery (El-Tahan 2011)

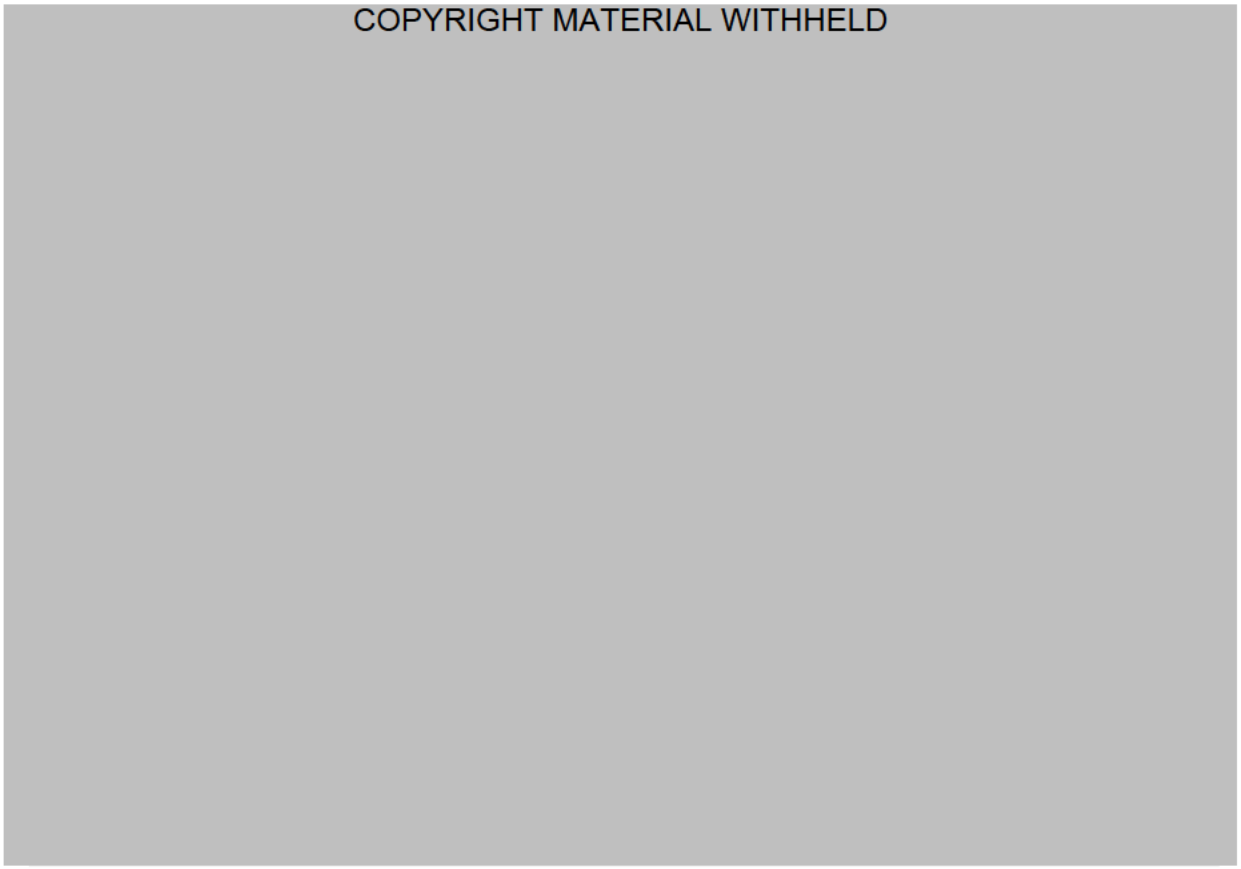
In this study, phenylephrine seems to have little effect in HR as the figure below:

HR during Surgery (El-Tahan 2011)



The incidence of hypotensive episodes during valve surgery, defined as mean arterial pressure ≤60 mm Hg for at least 2-3 minutes, decreased from 81% with placebo treatment to apparently nearly zero with phenylephrine as shown in the figure below.

Incidence of Hypotension (El-Tahan 2011)



Imran et al (2007)
Imran et al. (2007) reported on a prospective, randomized, double-blind, placebo-controlled evaluation of phenylephrine to attenuate anticipated hypotensive effects of intravenous propofol (general anesthesia). Patients undergoing elective surgery with propofol general anesthesia were administered phenylephrine 25 mcg/mL mixed directly with the propofol solution (n=44), phenylephrine 50 mcg/mL with propofol (n=45), or placebo/propofol (n=43). 2.5 mg/kg propofol were mixed in a 2 mL volume of 0.9% normal saline; therefore, the total administered doses of phenylephrine were 50 mcg (low dose) and 100 mcg (high dose). Hemodynamics were monitored over 6 minutes from induction of anesthesia. The principal efficacy endpoint was incidence of hypotension defined as ≥ 20% decrease from baseline systolic blood pressure before induction of anesthesia.

Phenylephrine blunted the hypotensive response to propofol at several time points after administration. Effects were noted for the primary efficacy endpoint systolic blood pressure, as well as for other hemodynamic endpoints including diastolic blood pressure, mean arterial pressure and heart rate as the table belwo. Statistically

significant benefits to reduce the hypotensive response to anesthesia were obtained between minutes 1-4 with the higher dose of phenylephrine, and at the 4 minute time point with the lower dose. The frequency of hypotension (defined as 20% decrease from baseline) was 20% with high-dose phenylephrine (100 mcg) vs. 51% with placebo control ($p<0.004$). The frequency of hypotension with low-dose phenylephrine (50 mcg) was 56%, not different from placebo. The authors concluded that coadministration of high-dose phenylephrine (100 mcg) with intravenous propofol is effective to attenuate anesthesia-induced hypotension.

Hemodynamic Effects of Phenylephrine (Imran et al. 2007)

A table of phenylephrine on SBP from the Imran publication is summarized as below:

Infusion

Allen et al. (2010)

Allen et al. (2010) reported on a prospective, randomized, double-blind placebo-controlled comparison of phenylephrine 25 mcg/min, 50 mcg/min, 75 mcg/min, 100 mcg/min or placebo for hemodynamic support during spinal anesthesia for Cesarean delivery. Women undergoing uncomplicated Cesarean deliveries were given intrathecal fentanyl/morphine/bupivacaine then immediately randomized to an intravenous phenylephrine or placebo (lactated Ringers only).

Study drugs were infused at 60 mL/hr with an additional fluid coload with the expectation that at least 2 L of fluid would be administered prior to delivery. Blood pressure readings were taken for the first 10 min after spinal injection and study drug administration then every 2.5 min thereafter. One hundred nine patients were recruited for the study, with 101 providing adequate hemodynamic data for analysis. (Eight patients did not complete the study due to inadequate or failed anesthesia.) After delivery, 5 units of oxytocin was administered as an IV bolus injection followed by an infusion of 25 U in 1 L lactated Ringer's solution given over 2 hours. Phenylephrine infusion was continued until 10 minutes after delivery.

The primary efficacy endpoint of this study was the number of physician interventions needed to maintain maternal systolic blood pressure within 20% of baseline and to treat bradycardia during the study period. Physician interventions, triggered by a decrease of systolic pressure by >20% of baseline or to <90 mm Hg, consisted of additional 100 mcg bolus phenylephrine infusions. None of the phenylephrine doses proved statistically superior to placebo in the number of physician interventions, although the highest dose (100 mcg/min) was statistically superior to two of the intermediate doses (25 and 50 mcg/min). However, several secondary hemodynamic endpoints were significantly affected with one or more test doses of phenylephrine compared to placebo. The general intent of phenylephrine use during anesthesia, i.e., reduction of the incidence of hypotension during surgical procedures, was demonstrated vs. placebo as shown in the table below.

Hemodynamic Variables after (b) (4) Phenylephrine (Allen et al. 2010)

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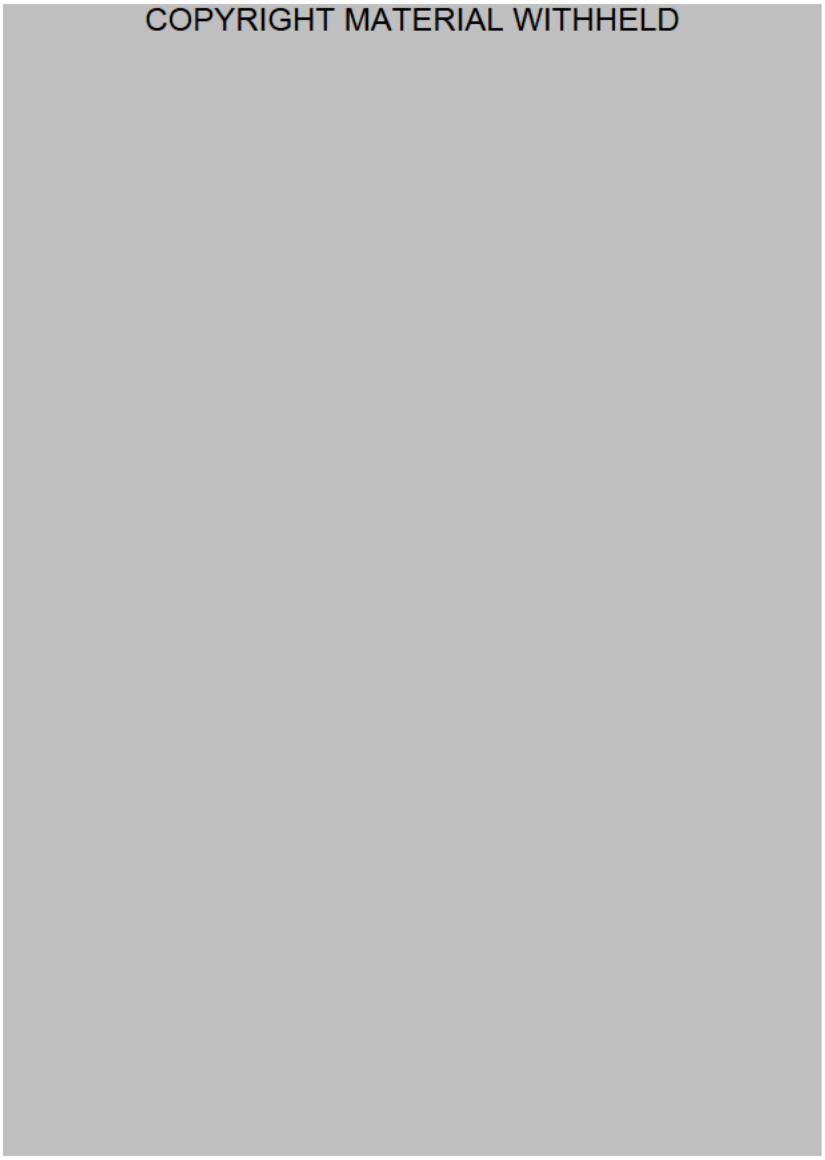
The magnitude of pressure effects of phenylephrine was also quantified by the median percentage performance error, defined as the difference between each measured value of systolic blood pressure and the baseline value, expressed as percentage of baseline for each patient. Median performance errors were <0 for patients in the placebo and low-dose (25 mcg/min) phenylephrine groups, and >0 in the three higher phenylephrine dose groups as shown in the figure below:

Effect of Phenylephrine on Mean Difference in SBP Compared to Each Patients' Baseline Value (Allen et al. 2010)



The authors concluded that although (b) (4) infusions of phenylephrine did not reduce the number of physician interventions needed to maintain maternal pre-delivery systolic blood pressure (the primary endpoint), (b) (4) phenylephrine infusion effectively reduced the incidence and severity of maternal pre-delivery hypotension. They further suggested that phenylephrine infusion rates of 25-50 mcg/min provided the best hemodynamic stability.

Langesaeter et al. (2008)

Langesaeter et al. (2008) report on a prospective, randomized, double-blind placebo-controlled evaluation of phenylephrine to [redacted] (b) (4) hemodynamic instability during Cesarean delivery. One hundred twenty-nine women were asked to participate in the study, 17 did not consent and 32 were excluded for various reasons (6 changed their mind, 8 postponed operation, 16 experienced technical difficulties with arterial line calibration, 2 due to “other problems”). Eighty women (20 per group) received either a high dose of bupivacaine/sufentanil spinal anesthesia (10 mg bupivacaine) or lower dose (7 mg bupivacaine), and either intravenous phenylephrine 0.25 mcg/kg/min or placebo. Phenylephrine or placebo solutions were infused for 20 minutes beginning at the time spinal anesthesia was induced. Additional intravenous phenylephrine bolus solutions (30 mcg) were administered as a rescue solution if systolic hypotension (< 90 mm Hg) developed. 5 U oxytocin was administered as a bolus dose after delivery.

The principal efficacy variables of the trial were systolic blood pressure and cardiac output after spinal anesthesia; other hemodynamic variables including mean arterial pressure and use of rescue phenylephrine or ephedrine were secondary variables. The authors proposed that a difference of 15 mm Hg systolic blood pressure between groups was clinically significant. Phenylephrine blunted the hypotensive effects (systolic pressure and mean arterial pressure over time) of spinal anesthesia, with increases in systemic vascular resistance and compensatory decreases in cardiac output. Effects of phenylephrine compared to placebo for combined anesthesia dose groups are shown in the figure below.

Hemodynamic Effects of Phenylephrine vs. Placebo (Langesaeter et al. 2008)

However, phenylephrine administration did not significantly reduce the use of rescue pressor drugs (administered when SBP < 90 mm Hg) (Table 36). When the individual anesthesia groups were evaluated with and without phenylephrine, the authors concluded that intravenous phenylephrine administered prophylactically with low-dose bupivacaine (with sufentanil) spinal anesthesia provided the optimal hemodynamic stability during Cesarean delivery.

Rescue Pressor Usage (Langesaeter et al. 2008)

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9.1.2 Non-placebo-controlled studies:

Bolus Injection during Neuraxia Anesthesia

Bjørnestad et al. (2009)

Bjørnestad et al. (2009) reported on a prospective, randomized, double-blind study in which (b) (4) bolus phenylephrine was compared to compression wrapping of the legs. Forty women scheduled for elective Cesarean sections were included in the study; twenty were randomized to each treatment group. It is concluded that phenylephrine maintained blood maternal blood pressure similarly to compression stockings.

Tanaka et al. (2009)

Tanaka et al. (2009) conducted a double-blind, up-down sequential allocation, modified by a variation of the Narayana rule. Fifty women were enrolled for the study. All 15 subjects who received 120 mcg phenylephrine were free from hypotension and nausea. The total dose of phenylephrine used in these patients ranged from 120 to 1800 mcg. Although 120 mcg was the highest dose tested in this study, the ED95 to (b) (4) hypotension was estimated to be 135 mcg, while 159 mcg was estimated to be necessary to (b) (4) both hypotension and nausea.

das Neves et al. (2010)

das Neves et al. (2010) compared therapeutic vs. (b) (4) phenylephrine regimens to maintain blood pressure control. It is concluded that (b) (4) continuous infusion of phenylephrine beginning immediately after the spinal block was the most effective approach to reduce the risk of maternal hypotension during Cesarean section.

Infusion during Neuraxia Anesthesia

There are several trials with active comparator (most commonly ephedrine) and trials without comparator, which will be briefly discussed below.

Ansari et al. (2011)

Ansari et al. (2011) compared the effects of two phenylephrine infusion rates combined with rapid crystalloid co-loading on (b) (4) hypotension during anesthesia. This randomized controlled trial included 117 women undergoing elective Cesarean sections. Each subject was administered 15 mg of hyperbaric bupivacaine 0.5% and fentanyl 20 mcg followed immediately by infusion of phenylephrine and co-loading with intravenous bolus of Hartmann's solution 10 (mL/kg). Initial infusion of phenylephrine was at a rate

of 60 mL/h with 54 women receiving 50 mcg/min and 63 women receiving 100 mcg/min. If after the first three minutes SBP was > 120% of baseline, the infusion was stopped. If SBP was between 80-100% of baseline, the infusion was continued at the same rate until delivery; rescue bolus doses of 50 mcg of phenylephrine were administered if blood pressure fell below 80% of baseline for two consecutive readings. Infusion was discontinued if SBP was > 100% of baseline or if bradycardia (heart rate < 50 beats/min) developed without hypotension.

The primary measure of efficacy was incidence of maternal hypotension; maternal bradycardia, total dose of phenylephrine used pre-delivery, incidence of nausea and vomiting, Apgar scores at 1 and 5 minutes and umbilical arterial and venous blood gases and base deficits were considered secondary outcomes.

It ws concluded that there was no difference in incidence of hypotension between the 50 mcg/min and 100 mcg/min groups.

Cooper et al. (2012)

Cooper et al. (2012) evaluated the efficacy of phenylephrine infusion at (b) (4) hypotension during spinal anesthesia for Cesarean section. One hundred women undergoing elective Cesarean sections received intravenous preload with 10mL/kg Hartmann's solution, followed by intrathecal administration of 0.5% hyperbaric bupivacaine 2.8 mL combined with diamorphine 400 mcg. Immediately following spinal injection, an intravenous infusion of phenylephrine was started at a rate of 67 mcg/min. The infusion rate was altered by doubling or halving with the aim of keeping SAP close to baseline and avoiding hypotension (SAP <80% of baseline), or hypertension (SAP >120% of baseline). The maximum allowable rate was 67 mcg/min. Any episode of hypotension determined by SAP or anesthetist's interpretation of symptoms was treated with a 100 mcg bolus of intravenous phenylephrine. Beginning three minutes after the start of phenylephrine infusion, the rate was halved if SAP was >110% and ≤120% of baseline for two consecutive readings; and hypertension was treated by stopping the infusion until SAP was <120% of baseline, at which point it was recommenced at half the previous rate. A 200 mcg bolus of intravenous glycopyrrolate was given if HR was <60 bpm and the SAP was <80% of baseline, or if the HR was <45 bpm.

It was concluded that the total dose of phenylephrine delivery by infusion was median 1000 mcg [range 670-1000]. Fifty-one patients required no change to the infusion rate (14 patients required one change, 21 patients required two changes, eight patients required three changes, three patients required four changes, and three patients required five changes). Fifteen patients were also given a single bolus of phenylephrine.

De Souza et al. (2011)

De Souza et al. (2011) evaluated the effects of continuous phenylephrine in patients receiving two different anesthetic doses. Sixty women received either 8 or 12 mg hyperbaric bupivacaine administered for spinal anesthesia, along with 5 mcg sufentanil

and 100 mcg of morphine. All subjects received 10 mL/kg Ringer's lactate prior to anesthesia. Phenylephrine infusion was initiated at a rate of 100 mcg/min and was subsequently adjusted to maintain blood pressure at baseline levels; infusion was stopped after fetal extraction. Blood pressure was automatically measured every three minutes. A 50 mcg bolus of phenylephrine was administered if SBP fell by more than 10% of baseline. The infusion was stopped if the patient developed hypertension (SBP >20% above baseline) and was restarted once SBP returned to baseline levels.

It was concluded that the total phenylephrine dose was mean 1024.3 mcg in the 12 mg bupivacaine group and 794.2 mcg in the 8 mg group. Incidence of hypotension and hypertension were similar between the two groups as was SBP.

Kee et al. (2004)

Kee et al. (2004) report on a prospective, randomized, single-blind study in which phenylephrine's ability to maintain SBP at 100%, 90% and 80% of baseline values was studied. Seventy-five women undergoing Cesarean sections were enrolled in the study and assigned to one of the three treatment groups. Spinal anesthesia was induced by 10 mg hyperbaric bupivacaine and 15 mcg fentanyl. Phenylephrine infusion (100 mcg/ml) was immediately started after anesthesia induction and continued for a minimum of 2 minutes. SBP and heart rate were measured at 1 minute intervals. Phenylephrine infusions were continued if SBP was ≤ the value of the preassigned study group (100%, 90% or 80% group). The infusion was stopped if SBP was higher than the assigned value. If SBP fell below the assigned level and was not corrected after 3 minutes, a 100 mcg bolus dose of phenylephrine was administered. Bradycardia that was associated with SBP less than baseline was treated with 0.6 mg atropine. After delivery, 5-10 IU oxytocin was given by slow IV injection.

It was concluded that phenylephrine effectively managed hypotension in this study and the incidence of nausea or vomiting decreased as patients were maintained closer to baseline levels.

Kee et al. (2008)

Kee et al. (2008) report on a prospective, randomized, double-blind active controlled study in which (b) (4) use of 100 mcg/mL phenylephrine infusion was compared with 8 mg/mL ephedrine infusion and various combinations of the two drugs. One hundred and twenty-five women were recruited to the study, and 122 completed the study. Hyperbaric 0.5% bupivacaine (10 mg) and fentanyl 15 mcg were used for anesthesia. Vasopressor infusion was initiated at the time of anesthesia induction at 60 mL/h and continued for 2 minutes unless SBP >120% of baseline. SBP was measured every minute, infusions were continued if SBP ≤ baseline and stopped if SBP > baseline. If more than two SBP measurements were hypotensive (SBP <80% of baseline), rescue IV bolus injection of 100 mcg phenylephrine was administered. Hypertension was defined as SBP >120% of baseline.

It was concluded that phenylephrine was effective at (b) (4) hypotension. The incidence of hypotension seen with phenylephrine alone was not different from that seen in the other groups.

Mohta et al. (2010)

Mohta et al. (2010) report on a prospective, double-blind comparison study in which the phenylephrine was compared to mephentermine in women undergoing scheduled Cesarean sections. Sixty women were enrolled in the study; 30 were assigned to each treatment group. Spinal anesthesia was induced by hyperbaric 0.5% bupivacaine (2.2 mL). (b) (4) vasopressor infusion was started immediately after anesthesia induction and blood pressure and heart rate were measured at 1 minute intervals. The starting dose of phenylephrine was 50 mcg/min. If hypotension occurred (SBP < 80% baseline or < 100 mm Hg, whichever was higher), a 100 mcg bolus dose of phenylephrine was administered. If SBP exceeded baseline values, the infusion rate was decreased in steps of 6 mL/h (5 mcg/min phenylephrine).

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In phenylephrine group, two patients developed hypotension during the study; the first patient experienced episodes at 6 and 30 minutes following anesthesia and required two bolus of phenylephrine for treatment, whereas the second patient had hypotension at 6 minutes that was treated by a single bolus.

Pinto et al. (2008)

Pinto et al. (2008) reported on a prospective, randomized, double-blind study to compare the effectiveness of (b) (4) intravenous infusion phenylephrine to interventional ephedrine in managing hypotension during spinal anesthesia for Cesarean section. Thirty subjects each were allotted to the test and control groups. For the test group, subjects received 34 to 67 mcg phenylephrine/minute starting immediately after anesthesia induction. For the control group, 5 mg bolus doses of ephedrine were administered in response to hypotension (SBP < 70% baseline).

(b) (4) infusion with phenylephrine showed a greater ability to maintain blood pressure within 30% of baseline compared to interventional bolus ephedrine dosing. However, the number of times a patient became hypotensive was higher in the phenylephrine group compared to the ephedrine group.

Sharrock et al. (1991)

Sharrock et al. (1991) report on a prospective, randomized study comparing (b) (4) infusions of phenylephrine to low-dose adrenaline. Thirty patients undergoing primary total hip replacement under lumbar extradural anesthesia with 0.75% bupivacaine (25 mL) were randomized to the two dose groups (dose levels were not specified). The vasopressors were administered to maintain MAP at 50 to 60 mm Hg. Hemodynamic measurements and arterial blood samples were obtained before anesthesia induction and at 10, 20, 30, 40, 50, 60 and 90 minutes thereafter.

Blood anesthesia levels were higher in the patients receiving phenylephrine compared to those receiving low-dose adrenaline. While phenylephrine and adrenaline had similar effects on MAP, phenylephrine caused a decrease in cardiac output and heart rate as expected with the activation of the baroreceptor response.

Stewart et al. (2010)

Stewart et al. (2010) was a prospective, randomized, double-blind study comparing 25 mcg/min, 50 mcg/min and 100 mcg/min phenylephrine infusions to maintain SBP during spinal anesthesia during Cesarean sections. Seventy-five women scheduled for elective Cesarean delivery were randomized to one of three dose groups. Spinal anesthesia was induced with 11 mg 0.5% hyperbaric bupivacaine and 15 mcg fentanyl. Phenylephrine infusions were started at the same time as anesthesia induction at a rate of 120 mL/h. The infusion was stopped if SBP went above baseline. Hypotension (SBP <80% of baseline for 2 consecutive measures) was treated with a 100 mcg bolus dose of phenylephrine. If no improvement was seen after two further consecutive readings, a 6 mg bolus dose of ephedrine was administered. Bradycardia (HR <50 bpm) for 2 consecutive readings was treated by stopping the phenylephrine infusion if the SBP was at or above the baseline, but if the SBP was below baseline, phenylephrine infusion was continued and a bolus of glycopyrrolate 200 mcg was administered. Blood pressure, heart rate and CO were measured every minute and presence of nausea and vomiting were assessed at 5 minute intervals until 20 minutes after spinal injection. Apgar scores and umbilical cord blood pH and blood gases were measured.

The 100 mcg/min dose was better at maintaining SBP at baseline levels than were the 25 and 50 mcg/min doses. The duration of infusion was inversely proportional to the dose, with a mean of 23, 27, and 31 minutes in the high, medium, and low dose groups, respectively. There were no differences in the number of interventions required due to hypotension or bradycardia, although there was a trend toward more interventions in the low dose group.

Van Elsen et al. (2009)

Van Elsen et al. (2009) presented the results of a prospective randomized trial conducted to compare phenylephrine and ephedrine in the (b) (4) of hypotension during anesthesia in a meeting abstract. The study included 97 women undergoing elective Cesarean deliveries; each was randomly assigned to receive a 20 mcg/mL/min infusion of phenylephrine or 1 mg/mL/min of ephedrine starting immediately after injection of spinal anesthesia. Maternal hemodynamic parameters, umbilical blood gases, Apgar scores and side effects (nausea, vomiting, dizziness) were compared between both groups. Hypotension (defined as MAP <80% baseline or <70 mm Hg) was treated with an intravenous bolus of 100 mcg of phenylephrine or 5 mg ephedrine, corresponding to treatment group assignment.

MAP remained relatively stable throughout the procedure for both groups of subjects. The only significant difference between the two groups was a higher MAP in the

phenylephrine group at 36 minutes post spinal puncture (T=18). There was no difference between the two groups in incidence of hypotension before and after birth.

Yoon et al. (2012)
Yoon et al. (2012) compared the effectiveness of phenylephrine infusion alone and phenylephrine combined with glycopyrrolate in maintaining hemodynamic stability in women undergoing spinal anesthesia for Cesarean delivery. Sixty women having elective Cesarean deliveries were administered 0.5% hyperbaric bupivacaine 10 mg and fentanyl 15 mcg injected intrathecally. Hartmann's solution was infused for 15 min without exceeding 1000 mL. The subjects were randomized to receive either a 50 mcg/min phenylephrine infusion or a 50 mcg/min infusion plus glycopyrrolate 0.2 mg injected intravenously immediately after spinal anesthesia. The infusion lasted for 15 minutes unless SBP was above baseline, at which time the infusion was stopped. Hypotension (SBP ≤ 80% of baseline SBP for 2 consecutive readings) was treated with a bolus of phenylephrine 100 mcg if HR > 60 bpm and a bolus of ephedrine 10 mg if HR < 60 bpm. Bradycardia (HR < 50 bpm for 2 consecutive readings) was treated by stopping the infusion if SBP was at or above baseline; if SBP was below baseline, a bolus of ephedrine 10 mg was administered.

There were no significant differences in SBP in either group compared to baseline or between the two groups (see Figure 16); SBP was maintained throughout the study period. In the phenylephrine-only group, five patients received phenylephrine rescue bolus and one patient received ephedrine rescue. In the phenylephrine plus glycopyrrolate group, four patients received phenylephrine rescue and one patient received ephedrine rescue.

Combined Bolus and Infusion for Treatment of Hypotension during Neuraxial Anesthesia
Hall et al. (1994)
Hall et al. (1994) report on a prospective, double-blind, randomized comparison of (b) (4) phenylephrine and two different doses of ephedrine. Thirty women scheduled for elective Cesarean sections were recruited to the study. Spinal anesthesia was induced by 0.5% hyperbaric bupivacaine (2.75-3 mL). A 2 mL IV bolus dose of vasopressor (20 mcg for phenylephrine, 6 mg for ephedrine groups) was administered immediately after anesthesia induction, and then infusions were started. Phenylephrine subjects received 10 mcg/min, while ephedrine doses were 1 and 2 mg/min. Maternal hemodynamics and neonatal Apgar scores were assessed.

Nine patients in the phenylephrine group became hypotensive (arterial pressure <20% SBP baseline), with the group as a whole spending approximately 52% of their time in the hypotensive range. A mean of 10 bolus interventional doses were required and a mean of 490 mcg (300-680 mcg) of phenylephrine were administered during the study.

9.2 Labeling Recommendations

DDMAC has tentatively accepted the proposed trade name Vazculep

Based on consultation from Pediatric and Maternal Health Staff, the labeling language proposed by the sponsor for Subsection 8.4 Pediatric Use should be removed and replaced by the following statement: "Safety and effectiveness in pediatric patients have not been established."

Based on consultation from Pediatric and Maternal Health Staff, the labeling language proposed by the sponsor for Subsection 8 Use In Specific Population should be removed and replaced by the following statement:

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Risk Summary
There are no adequate or well-controlled studies with PHENYLEPHRINE HYDROCHLORIDE INJECTION, [redacted] in pregnant women [redacted] animal reproduction studies [redacted] been conducted [redacted] it is not known whether [redacted], can cause fetal harm when administered to a pregnant woman. [redacted], should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Labor or Delivery
The most common maternal adverse reactions reported in published studies of phenylephrine use during neuraxial anesthesia during cesarean delivery include nausea and vomiting, [redacted] bradycardia, reactive hypertension, and transient arrhythmias. Phenylephrine does not appear to [redacted] alter either neonate Apgar scores or blood-gas status.

8.3 Nursing Mothers
It is not known whether phenylephrine is present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [redacted] and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Exercise caution when [redacted] is administered to a nursing woman.

9.3 Advisory Committee Meeting

There was no Advisory Committee held related to this NDA submission.

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

/s/

TIMOTHY T JIANG
03/20/2014

CHRISTOPHER D BREDER
03/20/2014
Agree with overall conclusions. See my CDTL memo for comments.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204300 **Applicant: Eclat** **Stamp Date: June 28, 2013**

Drug Name: Phenylephrine **NDA/BLA Type: Standard**

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.	X			
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). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) Did not reference approved product by West-ward. Base on literature only
DOSE					
13.	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: Study Title: Sample Size: Arms: Location in submission:	X			Based on literature only
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	X			Based on literature only

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	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			Based on literature only
16.	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			Based on literature only
17.	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					
18.	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			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	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	Non-chronic use
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	Based on literature only, Sponsor is unable to access source documents.
24.	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			
25.	Have narrative summaries been submitted for all deaths and			X	Based on literature

[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.

[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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				only, Sponsor is unable to access source documents.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	No special studies required
27.	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					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	Based on literature only, Sponsor is unable to access source documents.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	Based on literature only, Sponsor is unable to access source documents.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Based on literature only, Sponsor is unable to access source documents.
34.	Are all datasets to support the critical safety analyses available and complete?			X	Based on literature only, Sponsor is unable to access source documents.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	Based on literature only, Sponsor is unable to access source documents.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	Based on literature only, Sponsor is unable to access source documents.
37.	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	Based on literature only, Sponsor is unable to access source documents.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	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	Based on literature only

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes___

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

TIMOTHY T JIANG
08/26/2013

CHRISTOPHER D BREDER
08/26/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204300 **Applicant: Eclat** **Stamp Date: February 7, 2013**

Drug Name: Phenylephrine **NDA/BLA Type: Standard**

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.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?		X		See Non-Filable Comments #1 and #2
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		See Non-Filable Comments #2
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		See Non-Filable Comments #1
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). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) The Sponsor did not reference the approved product by West-ward. The submission is based only on literature
DOSE					
13.	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)?	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			The submission is based only multiple studies from the published literature

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	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			The submission is based only multiple studies from the published literature
16.	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			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		See Additional Comment following the Non-Filable Comments
SAFETY					
18.	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		See Non-Filable Comments #1 and #2
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	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	Non-chronic use
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
24.	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			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			X	No special studies

[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.

[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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				required
27.	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					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See Additional Comment below Non-Filable
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
34.	Are all datasets to support the critical safety analyses available and complete?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	The submission is based on literature only; The Sponsor is unable to access source documents.
37.	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	The submission is based on literature only; The Sponsor is unable to access source documents.
FINANCIAL DISCLOSURE					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	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	The submission is based on literature only; The issues in this Question are being evaluated as this literature is reviewed..

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _NO___

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

We recommend that this NDA not be filed because the following is met:

(d) FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:

(3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and 314.50 or 314.94.

Non-Filable Comments

The following comments should be conveyed to the sponsor.

1. You did not construct the Integrated Summary of Efficacy (ISE) adequately. Your ISE contains essentially two tables, which listed efficacy results of each individual study (publication) for the indications of treatment, (b) (4) of hypotension during anesthesia, respectively.

   For the ISE, we recommend that you follow Draft Guidance to Industry "Integrated Summary of Effectiveness" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf.

   As the NDA is based solely on literature, we also recommend that you follow appropriate section in the Guidance to Industry "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf

2. You did not construct the Integrated Summary of Safety (ISS) adequately. Your ISS contains essentially two tables, which listed safety results of each individual study (publication) for the indications of treatment, (b) (4) of hypotension during anesthesia, respectively, and tables of AERS database.

For the ISS, we recommend that you follow Reviewer Guidance "Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf.

Additionally, we emphasize that discussion of major safety results such as death if any, non-fatal serious adverse events, and common adverse events is an essential part of the ISS. Since you did not do this, we are unable to adequately determine how you derived adverse events in your proposed labeling.

We note that you discussed Age, Race, and Pediatric in Section 2.7.4 Summary of Clinical Safety (pages 80 to 81) which could be considered as components of ISS. However, discussion of Age, Race and Pediatric must be separated for the indications of treatment (b) (4) (See Comment 3).

3. Since your NDA has two indications (for treatment, (b) (4) of hypotension during anesthesia), each indication you propose should be in a separate subheading in ISE and ISS. We recommend you follow the advice on the Minutes of EOP2 meeting Q15 regarding how to organize the NDA.

   Separating of different indications in one NDA for ISE, and ISS is detailed in the Draft Guidance to Industry "Integrated Summary of Effectiveness", and in Reviewer Guidance "Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review", respectively.

Additional comment:
Some of publications submitted are studies conducted outside USA; you must submit a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission.

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

TIMOTHY T JIANG
04/04/2013

CHRISTOPHER D BREDER
04/04/2013