CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204300	Submission Date: 6/28/13;
Submission Type; Code:	505(b)(2);
Brand/Code Name:	Phenylephrine Hydrochloride Injection, USP 1%
Generic Name:	Phenylephrine Hydrochloride Injection
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Éclat Pharmaceuticals, Inc.
Relevant NDA(s)	-
Relevant IND(s):	Pre-IND 114033
Formulation; Strength(s):	Intravenous injection
Proposed Indication:	Treatment (b) (4) of hypotension during anesthesia
Proposed Dosage Regimen:	Intravenous bolus or infusion titrated to effect;

Indication	Route	Dose
Treatment of hypotension during anesthesia	Bolus injection:	40 µg to 100 µg every 1-2 minutes as needed, not to exceed 200 µg.
	Intravenous infusion:	10 µg/min to 35 µg/min, titrating to effect, not to exceed 200 µg/min.
(b) (4)	(b) (4)	(b) (4)

Table of Contents

---

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application for Phenylephrine Hydrochloride injection. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CP Findings

Éclat Pharmaceuticals re-submitted a New Drug Application (NDA) for phenylephrine (PE) HCl Injection 1% (10 mg/mL), USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. Previously, 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 4/5/13, regarding their original application submitted on 2/8/13. The current application is a re-submission of the original application with revisions to Integrated Summary of Efficacy and Integrated Summary of Safety sections. The proposed indication is for the treatment (b) (4) of hypotension during anesthesia, as a bolus or as a continuous infusion.

The approval of 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 PE Hydrochloride 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 PE HCl injection. The Applicant stated, however, that they are referencing information included in DMF (b) (4) for PE hydrochloride and the USP monograph for PE hydrochloride injection.

Many studies in the literature suggested that PE dose is often titrated ("titrate to effect") to achieve the desired effect (to maintain or increase in patient's blood pressure during surgery) and involves repeated administration. The differences in PE dose(s) needed in a patient may depend on a patient's sensitivity to PE. As such, the proposed doses of PE range from 40 µg to 100 µg every 1-2 minutes as needed, not to exceed 200 µg, and, 10 µg/min to (b) (4) µg/min, not to exceed 200 µg/min., for bolus and infusion, respectively. Typically, adjustments beyond the starting dose recommendations are left to the practitioner's discretion and the patient's needs.

With respect to safety and effectiveness in pediatric patients, the dosing recommendations have not been established; no studies were identified that evaluated the use of PE for the sought after indication. It is noted that the Applicant seeks waiver in pediatric patients from age 0 to (b) (4) years of age. On 3/5/14, during Pediatric Review Committee meeting, the committee members acknowledged the Applicant's rationale and agreed with the Applicant's proposal for ages 0 to <12 years. However, for ages =≥12 to 16 years, a deferral was suggested and will be granted.

The pertinent factors in this application may be to address PE doses (both bolus and infusion), keeping in mind of how the PE is administered, i.e., titrated to effect, used as per the clinical setting, PE dosage adjustment, if necessary, in special populations and drug-drug interactions during anesthesia.

Pharmacokinetic information

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.

PE Dosing information

The following PE dosing information is presented in order to orient the reader to PE doses used the clinical setting described in the literature. For further discussion on the efficacious dose of PE for either treatment [redacted] (b) (4) of hypotension during anesthesia, the reader is refer to medical officer's review as well as sections below (Sections 2.2.2 and 2.2.3), which PE's pharmacodynamic-dose relationship was discussed/elucidated.

The Applicant is proposing to limit the PE dose to 200 µg or 200 µg/mL. According to the literature reviewed, the Applicant's proposal appears to be acceptable.

Bolus PE

The Applicant presented the PE doses from the following literature information (Table 1) used in treatment of hypotension. Bolus PE doses range from 50 to 1000 µg. See Section 2.2.2 for further information.

Table 1: Literature information on PE doses used in treatment of hypotension

Literature	Dose used
Goertz et al. 1993a	~ 148 µg (2 µg/kg)
Goertz et al. 1993b	~ 72 µg (1 µg/kg)
Dyer et al. 2008	50-100 µg, repeated every minute as needed
Dyer et al. 2009	80 µg
Ishiyama et al. 2003	~112 µg (2 µg/kg)
Alahuhta et al. 1992	100 µg bolus (followed by 100 µg bolus)
Schwinn and Reves 1989	50, 100, 150, 200 µg
Thomas et al. 1996	Mean 600 µg (100 to 1000 µg)
George et al. 2010	80 to 180 µg

Infusion PE

The Applicant presented the PE doses from the following literature information (Table 2) used in reversal of hypotension. Infusion PE doses range from 0.15 to 4 µg/kg/min. See Section 2.2.2 for further information.

Table 2: Literature information on PE doses used in reversal of hypotension

Literature	Dose used
Butterworth et al. 1990	0.15 µg/kg/min (~10 µg/min) 0.30 µg/kg/min (~20 µg/min) 0.45 µg/kg/min (~30 µg/min)
Martinsson et al. 1986	0.5, 1.0, 2.0 and 4.0 µg/kg/min for 6 min
Nygren et al. 2006	0.50 ± 0.22 µg/kg/min (range, 0.21± 0.94 µg/kg/min)

Special populations

The Applicant did not conduct any pharmacokinetic studies. Instead they are relying on pharmacodynamic information (e.g., blood pressure, mean arterial pressure) that can be found in the literature and other sources to support the proposed labeling. In all, the literature information evaluating the impact of age, sex, and race on blood pressure response of PE is inconclusive or not adequate to suggest dosing recommendations.

Phenylephrine is primarily metabolized in the liver and eliminated in the urine. In patients with hepatic and renal impairment, one may expect that PE's pharmacokinetic properties can be altered and that PE responsiveness may be abnormal. End stage renal disease has been associated with altered hemodynamic effects as a result of the pathophysiology or treatment of renal failure.

In patients with end stage renal disease (ESRD), dose-response data indicate increased responsiveness to PE. 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

However, in contrast to renal impairment, literature suggests that in patients with liver cirrhosis, dose-response data indicate decreased responsiveness to PE. Higher doses of PE 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.

Drug-Drug interaction of PE

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.

The majority of studies described a pharmacodynamic response (e.g., blood pressure, mean arterial pressure) of PE as variety of medications may affect the sensitivity of tissue α-adrenoreceptors and either increase or decrease vasopressor effect of PE. An exception to above is of monoamine oxidase inhibitors (affecting PE's metabolism), which may increase the systemic PE concentrations, due to the fact that PE is primarily metabolized by monoamine oxidase. A review of the literature revealed that reserpine has also been reported to affect PE 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 PE. The following class of drugs may increase vasopressor activity of PE and lower dose of PE 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 PE and higher dose of PE 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 PE; atropine, steroids, norepinephrine transporter inhibitors and methylergonovine maleate may enhance PE's pressor effect and lower dose of PE may be needed. However, higher dose of PE may be needed when centrally acting sympatholytic agents (e.g., reserpine, guanfacine) as they may decrease the PE's pressor effect.

In all, from a clinical pharmacology perspective, the adequacy of the literature information presented in the application for the product labeling purpose is acceptable. There are no comments/information requests to be conveyed to the Applicant at this time.

2 QBR

2.1 General Attributes of the Drug and Drug Product

Phenylephrine was patented in 1934 (Thiele et al. 2011b) and has been used for a variety of indications for over more than 60 years (Thiele et al. 2011a) in clinical practice. Phenylephrine has been used as a component to treat many conditions such as nasal congestion (oral and intranasal medications), mydriasis (intraocular formulations), and for local vasoconstriction (topical formulations).

2.1.1 What is the to-be-marketed formulation?

Phenylephrine Hydrochloride Injection, USP, 1% (10 mg/mL) is a sterile, non-pyrogenic solution intended for intravenous use. The fill volumes are 1 mL, 5 mL and 10 mL in suitable glass vials fitted with gray rubber stoppers, (b) (4). The composition of the to-be-marketed drug product is provided in Table 3.

Table 3: Composition of Phenylephrine Hydrochloride Injection, USP, 1%

Component	Purpose	Quantity (per mL)	Quality Standard
Phenylephrine HCl	API	10 mg	USP, Ph. Eur., JP
Sodium chloride	(b) (4)	3.5 mg	USP-NF, Ph. Eur., JP
Sodium citrate dihydrate	(b) (4)	4 mg	USP-NF, Ph. Eur., JP
Citric acid monohydrate	(b) (4)	1 mg	USP-NF, Ph. Eur., JP
Sodium metabisulfite	(b) (4)	2 mg	USP-NF, Ph. Eur., JP
Sodium hydroxide	pH adjustmenta	As needed	USP-NF, Ph. Eur., JP
Hydrochloric acid	pH adjustmenta	As needed	USP-NF, Ph. Eur., JP
(b) (4)	(b) (4)	(b) (4)	USP-NF, Ph. Eur., JP
(b) (4)			

Recently PE hydrochloride injection (NDA 203826; Phenylephrine Hydrochloride; West Ward Pharm Corp.; 10 mg/mL solution; intravenous/infusion; See Table 2) was approved on 12/20/12, indicated for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia. The Applicant stated that West Ward (b) (4) for PE hydrochloride.

According to the Applicant several companies are currently marketing unapproved PE hydrochloride injection (Table 4) for the treatment of hypotension as well as other indications such as vascular failure in shock and paroxysmal supraventricular tachycardia (PSVT). It is noted that the Applicant's formulation contains (b) (4) to that of the West Ward formulation. It is also noted that there are no or minor differences in formulations, in particular, (b) (4) In all, the formulations on the market seem to be same, if not, extremely similar to each other.

(b) (4)

The Applicant stated (confirmed during the review of the submitted literature) that the majority of the published clinical pharmacology, efficacy and safety trials do not identify the manufacturer or the trade name of the PE drug product. The only studies that identified the trade name or supplier of the PE were Schmidt et al 2003., Neo-Synephrine, Abbott Laboratories (2003), Schwinn and Reves 1989, Winthrop Laboratories, New York, NY, and Sudano et al. 2007, Farmigea (S.p.A). The Applicant stated that based on information available, e.g., acquisition of Winthrop Laboratories by Abbott Laboratories, they suspect that Winthrop and Abbott formulations are identical. No information was submitted on Farmigea formulation. With respect to other formulations used in the literature, the Applicant suspects that one or more of the marketed products were used in studies in the literature.

Since the Applicant's as well as marketed products are a parenteral product intended for intravenous administration (bioavailability is self-evident) and it seems that formulations do not contain ingredients that would affect the bioavailability or phamacokinetics of PE, it appears that the submitted literature information will be sufficient to meet the clinical pharmacology requirement.

2.1.2 What are the proposed dosage and route of administration?

Phenylephrine Hydrochloride Injection is a parenteral product intended for intravenous administration. It is injected intravenously either as a bolus or in a diluted solution as a continuous infusion. The Applicant proposed the following dosage forms and strengths, dosage regimen for the (b) (4) treatment of hypotension.

Dosage forms and strengths

1. 1 mL single use vials containing 10 mg PE hydrochloride (10 mg/mL)
2. 5 mL pharmacy bulk package vials containing 50 mg PE hydrochloride (10 mg/mL)
3. 10 mL pharmacy bulk package vials containing 100 mg PE hydrochloride (10 mg/mL)

Proposed Dosing Regimens

The dose should be adjusted according to the pressor response (i.e. titrate to effect). Dilute before administration (Table 5).

Table 5: Indications and proposed doses

Indication	Route	Dose
Treatment of hypotension during anesthesia	Bolus injection:	40 µg to 100 µg every 1-2 minutes as needed, not to exceed 200 µg.
	Intravenous infusion:	10 µg/min to 35 µg/min, titrating to effect, not to exceed 200 µg/min.
(b) (4) (b) (4)	(b) (4)	(b) (4)

2.2 General Clinical Pharmacology

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

No clinical trials were conducted by the Applicant.

2.2.2. Is there a relationship between phenylephrine concentration and pressor response (blood pressure)?

Many studies in the literature suggested that PE dose should be adjusted according to the pressor response, i.e., titrate to effect. In other words, PE has been utilized and administered 'as-needed' basis in patients who are undergoing surgery, in order to maintain or increase in patient's blood pressure. The differences in PE dose(s) needed in a patient may depend on a patient's sensitivity to PE. Phenylephrine dose is often titrated to achieve the desired effect and involves repeated dosage adjustments (Cooper 2008, George et al. 2010).

The onset and duration of action of PE appear to be within seconds and lasts until minutes after administration (see Section 2.2.1.2 for further information). Although PE's onset and duration of action is 'rapid' and 'short,' a positive relationship between PE dose and an increase in blood pressure has been observed.

Butterworth et al. 1990, showed that mean arterial pressure (MAP) increased with increased PE dose administered as infusion. However, with in the same dose administered, increasing the duration of infusion of PE did not increase MAP substantially (Table 6).

Table 6: Pressor response to phenylephrine dose

Phenylephrine dose	Duration of Infusion (min)	Baseline MAP (mm Hg)	Post-dose MAP (mm Hg)	Δ MAP (mm Hg)
0.15 µg/kg/min (~10 µg/min)	4	83 ± 2	85 ± 2	2
	8		85 ± 2	2
0.30 µg/kg/min (~20 µg/min)	4		88 ± 3	5
	8		89 ± 2	6
0.45 µg/kg/min (~30 µg/min)	4		94 ± 2	11
	8		97 ± 2	14

Martinsson et al. (1986) reported that PE pressor activity is dependent on the concentration of PE infused. In the study, healthy young subjects (n=9) who were given sequentially increasing infusions of PE hydrochloride, 0.5, 1.0, 2.0 and 4.0 µg/kg/min (corresponding to 0.41, 0.82, 1.64, and 3.28 PE base µg/kg/min) for 6 min at each dose level resulting in PE mean plasma concentrations (immediately after infusion) of 20 (range 15 – 31) , 56 (30 – 78), 118 (74 – 157) and 308 (213 – 465) nM, respectively (Figure 1). Accordingly, when systolic blood pressures (upper curve) and diastolic blood pressures (lower curve) were plotted against PE concentrations, both systolic and diastolic pressures increased with increasing PE concentrations (Figure 2).

Figure 1: Phenylephrine concentrations after 0.5, 1.0, 2.0 and 4.0 µg/kg/min phenylephrine infusion rates

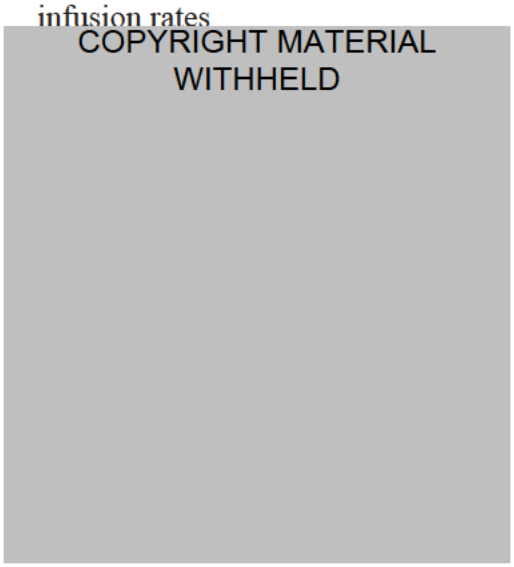
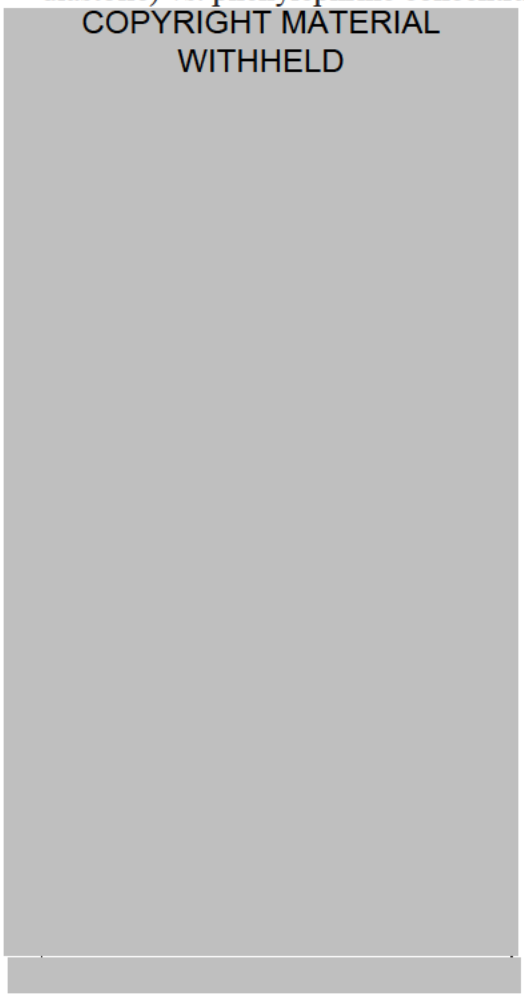


Figure 2: Blood pressure measurements (top panel; upper curve – systolic; lower curve - diastolic) vs. phenylephrine concentrations. (note: Plasma NA – plasma noradrenaline)



Many studies reported that PE pressor activity dependents on PE dose infused or PE plasma concentrations. The Applicant submitted the blood pressure responses to PE bolus injection and continuous infusion (Table 7 and Table 8, respectively) below. The overall information

suggested that pressor responses were in the 6 - 30 mm Hg range when bolus PE was administered with or without following PE infusion.

Table 7: Blood pressure response to phenylephrine bolus intravenous injection (SBP: systolic blood pressure; SAP: systolic arterial pressure; MAP: mean arterial pressure)

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

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)

2.2.3. Pharmacodynamics of phenylephrine

2.2.1.1 What is the known mechanism of action of phenylephrine?

Phenylephrine is an α1-adrenergic receptor agonist, acting as a strong post-synaptic α-receptor stimulant and produces a synthetic sympathomimetic effect. It has little to no activity on α2 or β- receptors (Hardman et al. 2001, Thiele et al. 2011a, Thiele et al. 2011b). Phenylephrine is a synthetically formed from epinephrine; PE lacks a hydroxyl group at position 4 on its benzene ring (Thiele et al 2011a) (Figure 3).

Figure 3: Epinephrine and phenylephrine structures.

The primary site of action of PE is in the vasculature and α1 receptor is its main target. Activation of α1 receptors, particularly in arterial blood vessels, by PE increases activation of the vascular smooth muscle cells, and, thus vascular smooth muscle contraction, producing increases in systolic and diastolic pressures as well as the mean arterial pressure ('vasopressor effect') (Thiele et al. 2011a). 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).

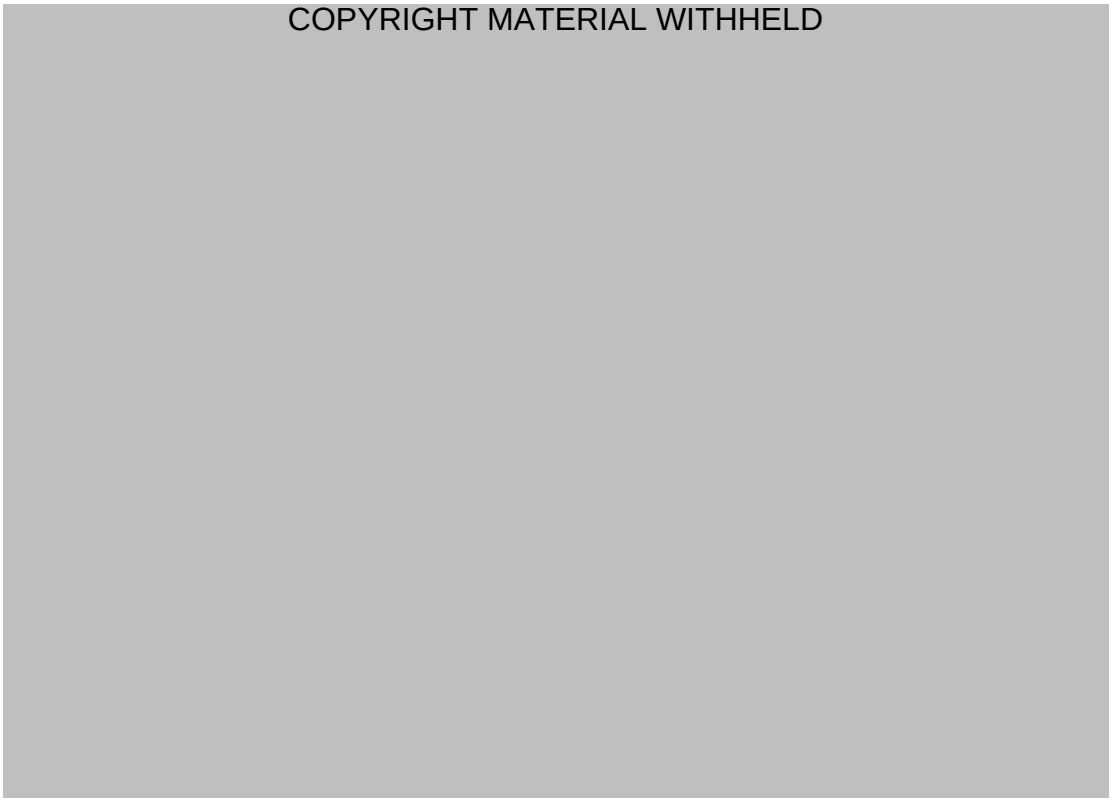
However, PE is known to have a modest effect on the heart itself as decrease in both heart rate (reflex bradycardia) and cardiac output is observed (due to the increase in afterload) (Thiele et al. 2011a; Nygren et al. 2006). The effects are considered to be concentration dependent and somewhat variable from individual to individual (Martinsson et al. 1986).

Additionally PE is known to have activity on renal, pulmonary and splanchnic arteries but likely only has minimal to no effects on cerebral vessels due to inability to cross the blood brain barrier. (Johnston et al. 1994, Ishiyama et al. 2003). Phenylephrine was reported to have local (topical) effects on α-adrenergic receptors in the eye causing mydriasis (Meyer and Fraunfelder 1980).

2.2.1.2 What is the known onset and duration of action of phenylephrine on blood pressure (a primary response)?

The onset and duration of action (blood pressure and heart rate) of PE are rapid. The Applicant submitted supportive information looking at the effects of bolus 10 mg of ephedrine or 80 µg of PE on maternal cardiac output, heart rate and mean arterial pressure (Dyer et al 2009). Patients (n=40) were scheduled for elective cesarean delivery under spinal anesthesia. Ephedrine and PE was administered as the initial vasopressor for the management of hypotension during spinal anesthesia. 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 4: Percent changes from pre-vasopressor values in cardiac output (CO), heart rate (HR) and mean arterial pressure (MAP)



As presented below, PE effects were mainly on the peripheral vasculature rather than on the heart (Table 9). Mean arterial pressure decreased before PE administration.

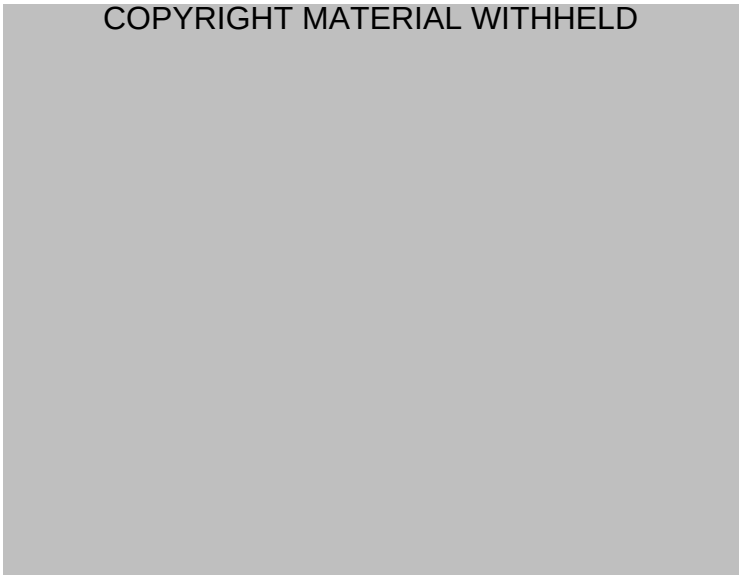
Table 9: Summary of systemic effects with phenylephrine (Dyer et al. 2009)

	Baseline ± SD	**Pre-vasopressor ± SD**	**150 sec post-phenylephrine ± SD**
Heart Rate, beats per minute	80.4 ± 10.7	91.5 ± 17.6	76.9 ± 12.7
Mean Arterial Pressure (MAP); mmHg	91.5 ± 10.9	72.8 ± 7.1	86.3 ± 9.1
Stroke Volume; mL/beat	73.5 ± 18.2	80.2 ± 16.1	81.4 ± 17.2
Stroke Volume Ratio; Dyne *sec*cm^{-5}	1241.2 ± 266.9	782.6 ± 169.3	1123.7 ± 259.7
Cardiac Output (LiDCO)[a]; L/min	5.8 ± 1.2	7.2 ± 1.4	6.2 ± 1.3
Cardiac Output (BioZ);[b] L/min	4.6 ± 0.9	5.7 ± 1.6	5.2 ± 1.5

[a] Cardiac output derived using the LiDCOplus (LiDCO, Cambridge, United Kingdom) monitor
[b] Cardiac output derived using the BioZ (Cardio Dynamics International, San Diego, CA) monitor

Goertz et al. (1993a) reported similar findings with rapid increase in MAP after PE bolus intravenous injection. In a crossover, comparator controlled study, in which patients (n=16) were undergoing an elective minor abdominal or orthopedic surgery, received IV bolus doses of 2 µg/kg PE or 0.1 µg/kg norepinephrine in random order to treat hypotension under isoflurane anesthesia. The figure shows that MAP reached maximal value 30 seconds after application and returned to near baseline levels by 180 seconds after administration (Figure 5).

Figure 5: Mean arterial pressure (MAP) immediately before 0 and 30, 60, 120 and 180 seconds after bolus PE administration. (Arithmetic mean (95% Confidence interval))



2.2.4. Pharmacokinetics of phenylephrine

2.2.4.1. What are the PK characteristics of phenylephrine?

Pharmacokinetic information of PE in human is limited. According to Schering-Plough Corporation's document submitted to the Nonprescription Drugs Advisory Committee, November 19, 2007, titled, 'Understanding Phenylephrine Metabolism, Pharmacokinetics, Bioavailability and Activity,' when a single oral dose of 10 mg PE was administered, the exposure to parent-PE (drug itself) is in the orders of magnitude less than total-PE (parent and metabolites (glucuronidation and sulfation); see Section 2.2.4.2 for further information on metabolism). The parent-PE peaks within 30 minutes and decays rapidly compared to total-PE which has a much broader profile.

Hengstmann et al., 1982, studied the pharmacokinetics of tritiated phenylephrine (3H-PE) following an intravenous infusion or oral administration. One mg (mean dose of 0.84 ± 0.17 mg; n=4) was infused over 12.5 to 20 minutes in 4 healthy volunteers. Blood samples were taken out to 8 hours. Free 3H-PE was separated from serum by column chromatography. At the end of short infusion, the concentration curve showed that PE exhibited biphasic decline (Figure 6), as observed by an initial rapid distribution followed by relatively slow elimination (Table 10).

Figure 6: 3H-Phenylephrine concentration-time curve after short intravenous infusion; ● intravenous administration; ○ oral administration) (Hengstmann et al., 1982)

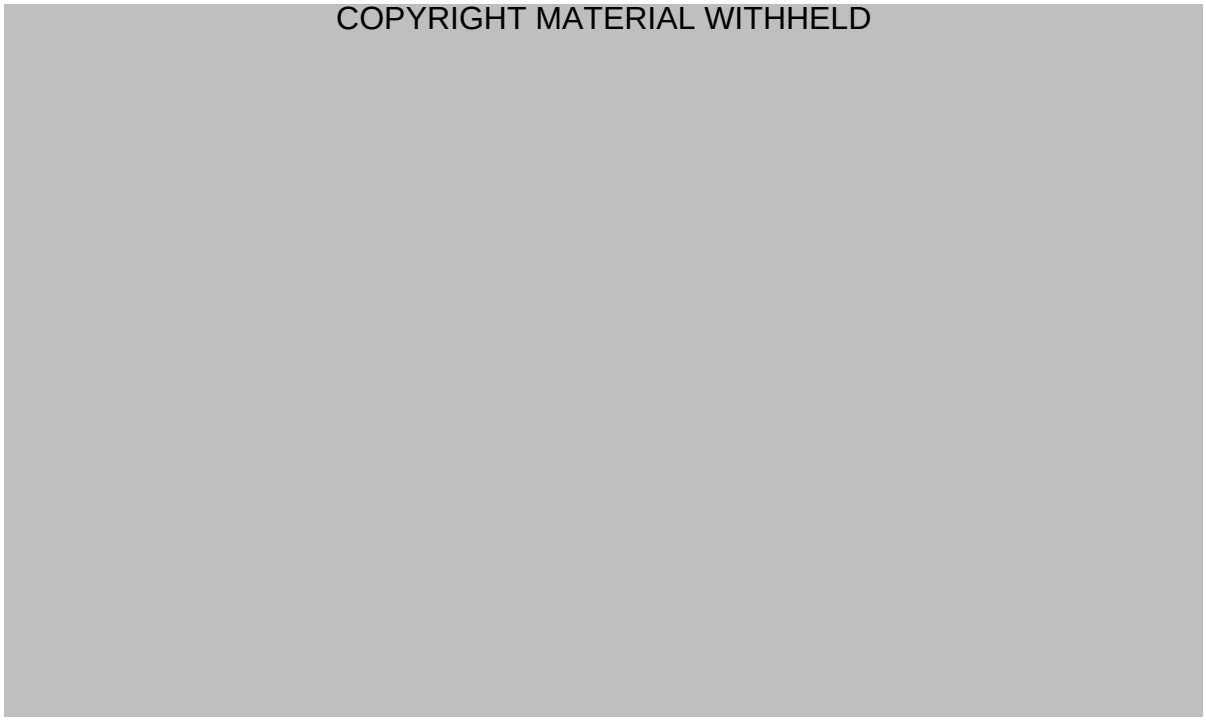


Table 10: Mean serum free 3H-PE levels (right panel) after intravenous infusion; n=4

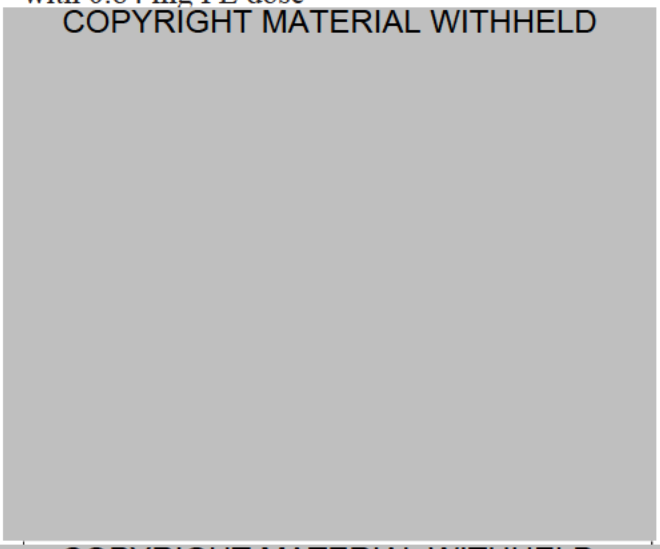
The free 3H-PE concentration-time curve was fitted to an open two-compartment model. Table 11 contains PE parameters obtained from the model. The authors stated that elimination half-life following infusion was 151 minutes (2.51 h based on β rate constant). The reported average steady state volume of distribution (Vss) was 340 L (range: 184 to 543 L).

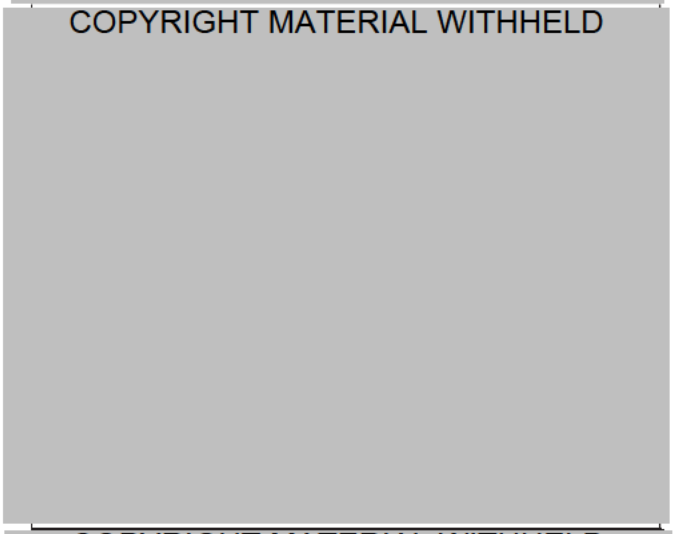
Table 11: Pharmacokinetic parameters after phenylephrine infusion

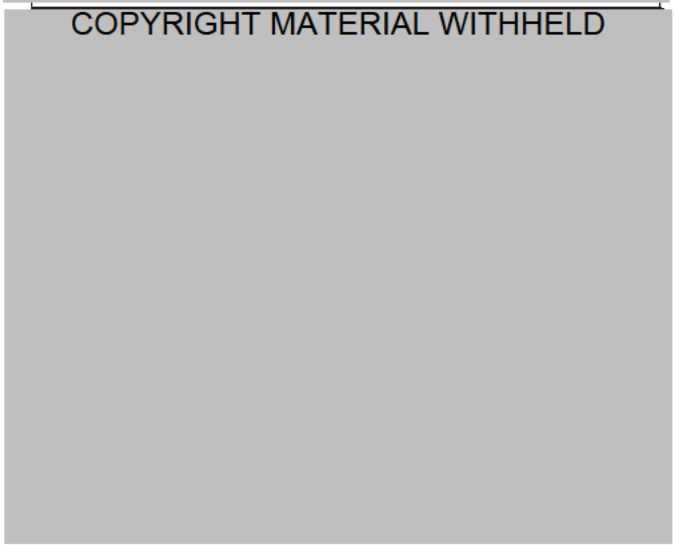
A (ng· mL-1)	B (ng· mL-1)	α (min-1)	β (min-1)	AREA (ng· min/mL)	kel (min-1)	Cltot (mL/min)	Clren (mL/min)	Vdss (L)
21.04 + 9.68	1.49 + 0.89	0.1527 + 0.0206	0.0046 + 0.0011	439.52 + 171.63	0.0512 + 0.0078	2095 + 814	539 + 170	340 + 174

To confirm, a simple modeling was conducted using WinNonlin (Version 6.3) program. The observed mean data (Table 12) from the article was fitted to a 2-compartment *i.v.* infusion model with first order elimination. It is noted that the pertinent information, such as individual infusion rate, duration, etc., was not specified in the article. Instead, in the confirmatory modeling step, a mean dose value of 0.84 mg and 3 infusion rates, 12.5, 15 and 20 minutes, were inputted into the model. The following figures (Figures 7, 8, and 9, for 12.5-, 15- and 20-minute infusion durations) were obtained from the model.

Figures 7, 8, and 9: 12.5-, 15- and 20-minute infusion time, top, middle, bottom, respectively, with 0.84 mg PE dose







The following pharmacokinetic parameters were obtained from the modeling (Table 12, 13, and, 14 for 12.5, 15 and 20 minutes, respectively).

Table 12: PE PK parameters using 0.84 mg dose and 12.5-minute infusion time

Parameter	Units	Estimate	StdError	CV%
K10	1/min	0.088142746	0.0078083284	8.8587306
K12	1/min	0.1633878	0.013191241	8.0735782
K10_HL	min	7.8639163	0.69480034	8.8352967
AUC	min*ng/mL	352.07102	21.872932	6.2126478
Alpha_HL	min	2.5683304	0.17982296	7.0015509
Beta_HL	min	77.876852	10.323156	13.255744
A	ng/mL	28.850346	1.724045	5.975821
B	ng/mL	2.1821608	0.16602051	7.6080786
Cmax	ng/mL	10.324062	0.16631299	1.6109259
CL	mL/min	2391.5629	149.03224	6.2315833
AUMC	min*min*ng/mL	30142.164	5923.8977	19.653193
MRT	min	79.363876	11.776658	14.838814
Vss	mL	189803.7	17703.318	9.3271719

Table 13: PE PK parameters using 0.84 mg dose and 15-minute infusion time

Parameter	Units	Estimate	StdError	CV%
K10	1/min	0.096885163	0.008491805	8.7648147
K12	1/min	0.15709843	0.012751565	8.1169269
K10_HL	min	7.1543171	0.6253814	8.7413151
AUC	min*ng/mL	373.9704	21.91006	5.8587684
Alpha_HL	min	2.5684137	0.17983873	7.0019377
Beta_HL	min	77.886093	10.324864	13.256364
A	ng/mL	34.026097	2.13714	6.2808848
B	ng/mL	2.2060862	0.17031457	7.7202139
Cmax	ng/mL	10.323896	0.16631375	1.6109592
CL	mL/min	2251.5151	132.34328	5.8779656
AUMC	min*min*ng/mL	31126.211	5978.4998	19.207284
MRT	min	75.731749	11.367343	15.01001
Vss	mL	170511.18	16707.19	9.7982963

Table 14: PE PK parameters using 0.84 mg dose and 20-minute infusion time

Parameter	Units	Estimate	StdError	CV%
K10	1/min	0.11215385	0.0095310506	8.4981926
K12	1/min	0.14511772	0.011954078	8.2375042
K10_HL	min	6.1803242	0.52375739	8.4745942
AUC	min*ng/mL	419.25173	22.047603	5.2587983
Alpha_HL	min	2.5693512	0.17986843	7.0005388
Beta_HL	min	77.909579	10.332895	13.262676
A	ng/mL	44.767048	2.9474984	6.5840803
B	ng/mL	2.2536495	0.17911856	7.9479333
Cmax	ng/mL	10.323987	0.16631599	1.6109666
CL	mL/min	2008.34	106.012	5.2785882
AUMC	min*min*ng/mL	33279.577	6089.321	18.297471
MRT	min	69.378509	10.586711	15.259353
Vss	mL	139335.63	14726.809	10.569306

The confirmatory modeling step reported an average steady state volume of distribution (Vss) of 139 to 190 L, a similar value reported by Hengstmann et al 1982. The distribution half-life (α-phase) was very short (<3 min), as it appears that an average 80% of PE is eliminated within ~10 minutes following cessation of the infusion. The terminal elimination half-life (β-phase) was 77 minutes.

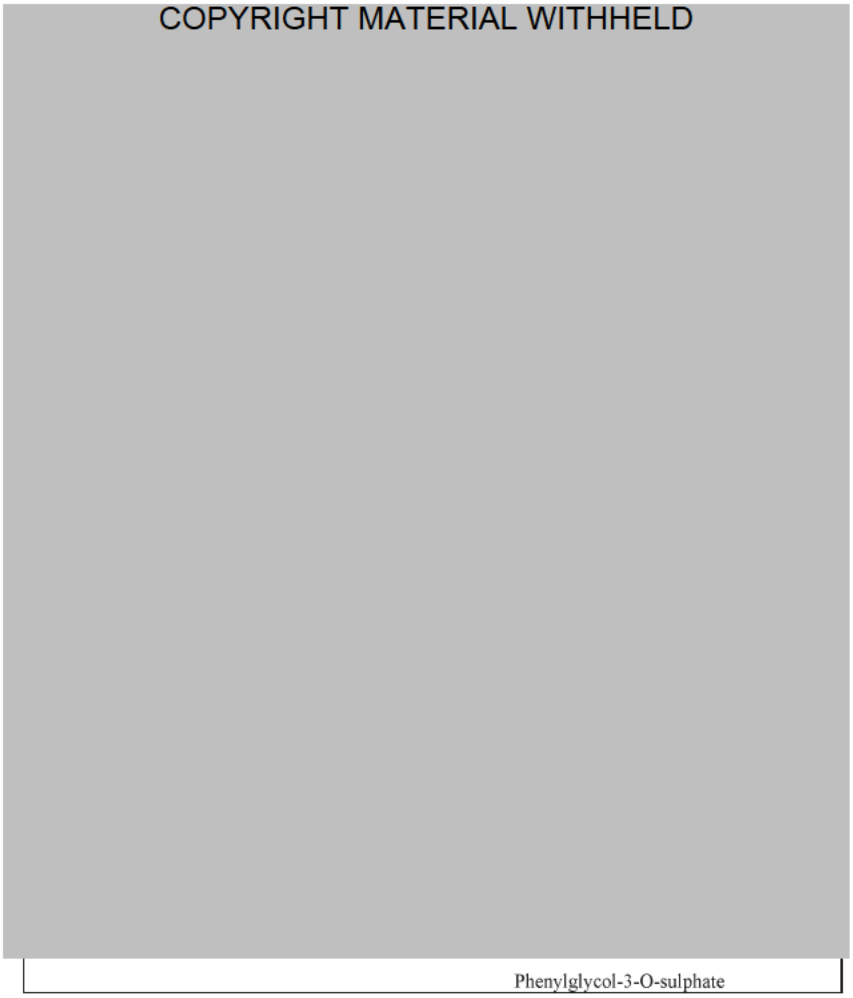
2.2.4.2. What are the characteristics of metabolism and elimination of PE?

Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. According to Hengstmann et al 1982, based on 3H-PE intravenous and oral 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. Due to the extensive metabolism, 16% of the dose was excreted unchanged (i.e., parent PE) in the urine at 48 h post intravenous administration. It is noted that the ratios of the metabolites produced differ depending on the route of administration (Table 15). There are two major metabolites with approximately 57 and 8% of the administered dose excreted as *m*-hydroxymandelic acid and sulfate conjugates, respectively.

Table 15: Cumulative urinary excretion of 3H-activity, free (PE) and metabolites after intravenous (n=3) and oral (n=10) administration of 3H-PE

Ibrahim et al. 1983 reported similar findings for an investigation of oral *m*-synephrine (PE, unlabeled). Using GC-MS analysis, the major urinary metabolites were *m*-synephrine sulfate (47%), *m*-hydroxymandelic acid (30%), *m*-synephrine glucuronide (12%) and *m*-hydroxyphenylglycol sulfate (6%). The proposed metabolic pathways after oral PE administration are shown in Figure 10. The metabolites are considered not pharmacologically active (Schering-Plough's Briefing Document 2007).

Figure 10: Metabolic pathways for PE. The values in the schematic refer to the percent of a 24.6 mg oral dose reported by Ibrahim et al 1983 (Schering Plough Briefing Document 2007).



2.3. Intrinsic Factors

No pharmacokinetic studies were conducted to evaluate PE in special populations such as geriatric, hepatic impaired and renal impaired patients. No pharmacokinetic studies were conducted to evaluate PE due to age, sex and race.

The Applicant did, however, submitted pharmacodynamics literature information to address each of the populations. The PE effect on systolic, diastolic, and arterial pressures were assessed. In all, the literature information evaluating the impact of age, sex, and race on blood pressure response of PE is inconclusive or not adequate to suggest dosing recommendations. Altered pharmacodynamics responses were observed in hepatic impaired patients and renal impaired patients. In patients with end stage renal disease (ESRD) undergoing hemodialysis, dose-response data indicates increased responsiveness to PE. In patients with liver cirrhosis, dose-response data indicate decreased responsiveness to PE.

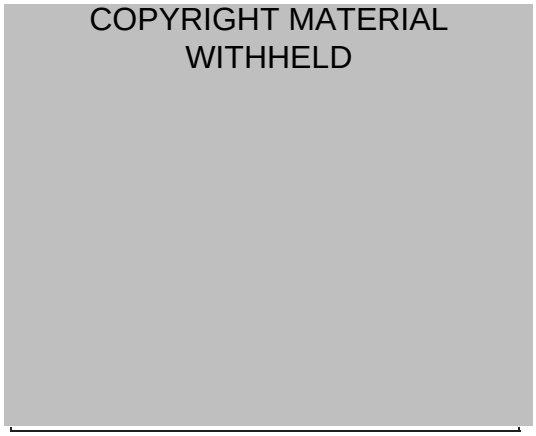
2.3.1. Age

Information regarding use of PE hydrochloride in the elderly population varies widely. White et al. 1999 reported that, in a baroreceptor study, a positive correlation of increased sensitivity to PE'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 PE based on measurements of systemic vascular resistance response to pressor infusion.

2.3.2. Race

Stein et al. 2000 studied the sensitivity to α-vasopressor and β-vasodilator in healthy normotensive young black and white subjects. Forearm blood flow was measured with strain-gauge plethysmography after intra-arterial administration of PE (1.25 to 20 μg/min) or isoproterenol, after application of lower-body negative pressure, and after a cold pressor test. Phenylephrine decreased forearm blood flow more in healthy young black subjects than in healthy young white subjects (Figure 11). At the 10 μg/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.

Figure 11: Percent decrease in forearm blood flow after intra-arterial infusion of 1.25 to 20 μg/mL PE in normotensive black and white subjects (mean ± SEM). (■ black; □ white subjects)



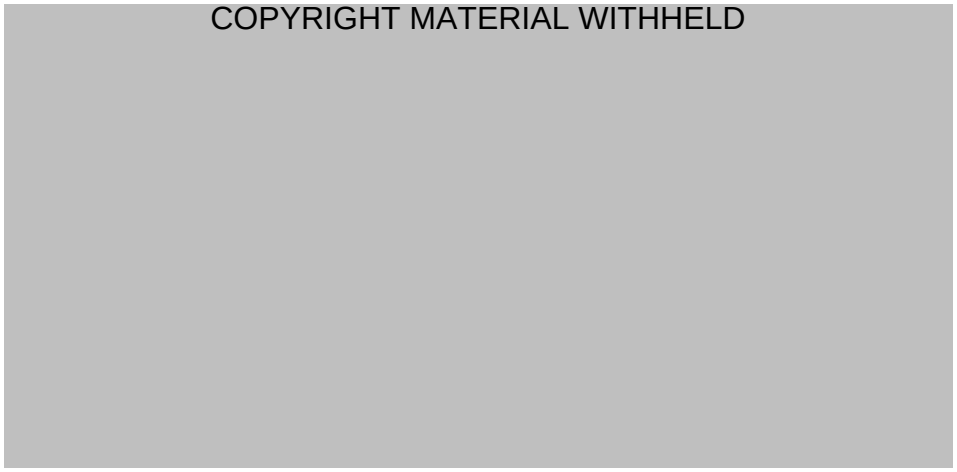
2.3.3. Sex

Wolzt et al. (1995) conducted a double-blind, randomized cross-over trial to compare the PE responses in healthy male and female volunteers. The trial compared hemodynamic effects of intravenous doses of PE, isoprenaline, sodium nitroprusside and placebo against baseline. Phenylephrine was administered as 10 minute infusion at 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 μg/kg/min. There was a significant sex difference for several of the hemodynamic parameters (systolic and diastolic blood pressures, pulse pressure, pulse rate) under baseline conditions; however, no difference in responsiveness to PE was reported. Additional information may be needed to support the findings.

2.3.4. Hypertensive

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). Phenylephrine was administered at 4 incremental rates (0.4-1.6 μg/kg/min) for 8 minutes each. 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 PE (Figure 12).

Figure 12: Change in systolic and diastolic blood pressure with PE: effect of age and existing hypertension



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). After infusion of PE 0.3, 0.6, and 0.9 μg/kg per minute, beat-to-beat arterial blood pressure, heart rate, postganglionic muscle sympathetic nerve sensitivity and baroreflex responses. 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 authors concluded that an association between obesity and hypertension triggers sympathetic activation and impairment in baroreflex cardiovascular control.

2.3.5. Hepatic Impairment

In patients with severe cirrhosis [Child-Pugh grade B (moderate) or C (severe disease)] and healthy subjects, PE hydrochloride was administered at rates ranging from 0.5 μg/kg/min to 6.0 μg/kg/min. The average rise in systolic, diastolic and mean arterial BP was calculated and plotted against the log of the dose. **A** log dose-response curve was constructed using a quadratic fit. From these curves the doses of PE required to raise BP by 10 mm Hg and 20 mm Hg (PD10 and PD20) were calculated for each subject. The results indicated that the cardiovascular

responsiveness (BP responses; Figure 13) to PE was attenuated in patients with severe cirrhosis (Table 16; PD measurements).

The dose of PE required to raise the blood pressure by 10 mm Hg was greater in patients with cirrhosis (1.25 µg/kg/min) than in controls (0.97 µg/kg/min). Similar findings were reported to raise the BP by 20 mm Hg, cirrhosis vs. controls (2.34 vs. 1.51 µg/kg/min, respectively) (MacGilchrist et al 1991). The bradycardia was observed during PE infusion, as an indicator of baroreceptor function of PE. The reduction in heart rate for a given rise in blood pressure ($\Delta HR/\Delta BP$) was 0.74 ± 0.49 in cirrhotic patients and 0.38 ± 0.25 in controls.

Table 16: Cardiovascular responses to PE

COPYRIGHT MATERIAL WITHHELD

Figure 13: Increase in BP in response to PE – log PD10 and PD20. The dose-response curve of the cirrhotic patients is shifted to the right.

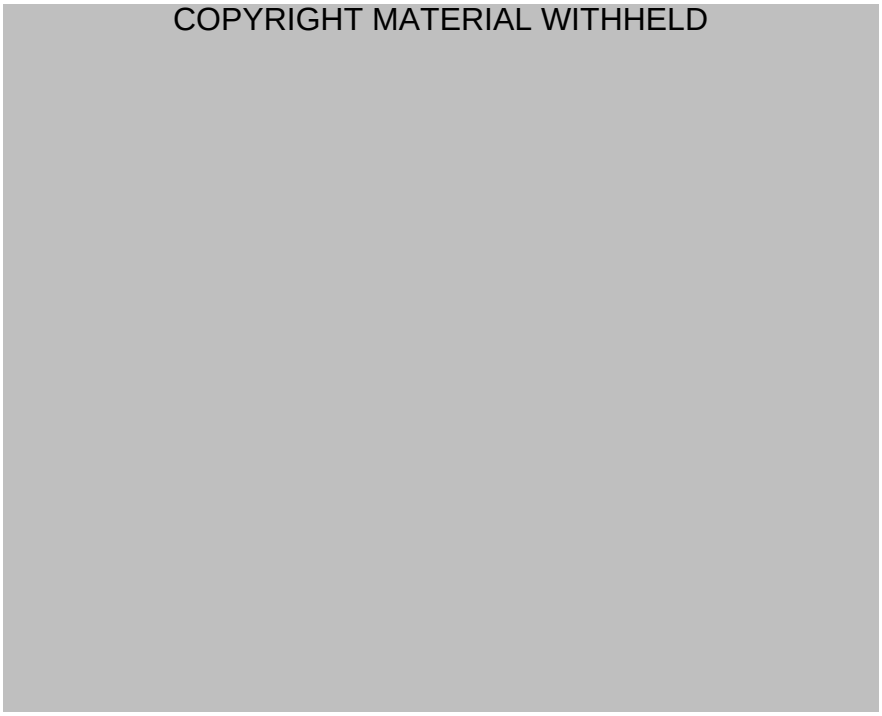
COPYRIGHT MATERIAL WITHHELD

2.3.6. Renal impairment

In patients with end-stage renal disease (ESRD) on erythropoietin treatment [recombinant human erythropoietin (rHuEPO)] the responsiveness of PE (vasopressor) on bradykinin (vasodilator) was assessed using the dorsal hand vein technique (Abiose et al. 2007). Phenylephrine was infused (minimum of 7 minutes) in the dose range of 0.75 to 7917 ng/min and the dose producing almost total constriction was determined. Individual dose-response curves to PE were fitted to a 4-parameter logistic regression equation [estimates of the maximal response (Emax) and of the potency (ED50, dose at half-maximal effect)]. It has been noted that rHuEPO demonstrated a direct vasoconstrictor effect on vascular smooth muscle cells in vitro. However, in the study, the authors could not demonstrate the vasoconstrictive effect of rHuEPO in healthy volunteers (in hand veins).

The results indicated that PE produced dose-dependent vasoconstriction in the hand veins in both the patients with ESRD and in the healthy control group. There was a shift of the D-R curve to the left in patients with ESRD compared with healthy subjects (Figure 14), indicating that sensitivity to the PE was significantly increased in patients with ESRD on rHuEPO. The mean dose of PE producing 50% venoconstriction (ED50) was 38 ± 1.6 ng/min in patients with ESRD and 145 ± 1.3 ng/min in healthy volunteers—approximately 4-fold increase in dose. Based on the information presented in this study using the dorsal hand vein, lower doses of PE may be potentially be required in patients with ESRD on rHuEPO. Overall, similar recommendation may be prudent in patients with renal impairment.

Figure 14: Representative dose-response curves of PE infusion rate vs. % vasoconstriction in a patient with ESRD and a healthy subject



2.3.7. What is the PE exposure in pediatric subjects?

The Applicant is requesting a waiver for the development of PE in pediatric subjects from age 0 to (b) (4) years of age. The Applicant stated that the studies necessary would be impossible or highly impractical (Table 17).

Table 17: The Applicant's justifications

Age group	Justification
0 to <12 years	1. While pediatric patients aged 0 to <12 years receive neuraxial anesthesia, they tend not to develop clinically significant hypotension as a result of anesthetic-induced vasodilatation. 2. The cardiac output of younger pediatric patients is heart rate-dependent, and administration of an alpha-1-receptor agonist would cause a reflex bradycardia, potentially decreasing the pediatric patient's cardiac output and oxygen delivery. More likely interventions, especially in children under 6 years, would be fluid administration, decreasing anesthetic concentration, or administration of a drug with beta-agonist effects, thereby increasing heart rate.
=≥12 to 16 years	1. Applicant is aware that a study is being conducted that evaluates the dose effect of PE hydrochloride injection on blood pressure in patients in this age group undergoing general anesthesia and neuraxial anesthesia. Thus, it would be unethical to conduct a study with the same objective in the same population.

The Applicant further stated that data from the literature demonstrate that pediatric population exhibit similar responses to intravenous PE hydrochloride injection.

Pediatric patients [n=16 young patients (mean age 13.1 years, range 7 years 10 months to 17 years 10 months) with recurrent syncope] underwent head-up tilt table testing, with or without 0.5 μg/kg/min PE infusion, to elicit a hemodynamic response. PE was incrementally increased until a 10-15 mm Hg increase in mean arterial pressure was achieved. Overall, however, PE was infused at an average rate of 1.74 μg/kg/min (range 0.6-3 μg/kg/min). In PE administered group, mean arterial pressure values increased an average of 14 mm Hg (96 ± 15 mm Hg with PE vs. 82 ± 13 mm Hg without studied (Strieper et al 1993)). It can be noted that, in this study, pediatric patients received a similar PE infusion rate compared to adults and the mean arterial pressure increase was also comparable to that of adult population (Table 9).

On 3/5/14, during Pediatric Review Committee meeting, the committee members acknowledged the Applicant's rationale and agreed with the Applicant's proposal for ages 0 to <12 years. However, for ages =≥12 to 16 years, a deferral will be granted.

2.4. Extrinsic Factors

2.4.1 Drug-Drug interactions

The Applicant did not conduct any 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. The majority of studies described a pharmacodynamic response of PE as variety of medications may affect the sensitivity of tissue α-adrenoreceptors and either increase or decrease vasopressor effect of PE. An exception is of monoamine oxidase inhibitors (affecting PE's metabolism), which may increase the systemic PE concentrations.

It is noted that the majority of studies employed variety of dosing schemes, e.g., PE infusion in divided doses starting with 0.02 mg/min which was increased by 0.01 mg/min at 5 minute intervals until diastolic pressure rose by 15 mm Hg (Mehta and Cohn (1977)), which add to the complexity of interpreting the relationship of PE's pressor effect in drug interactions. The complexity adds to developing a dose-adjustment in drug-drug interactions.

As stated above, PE will be administered in a controlled surgical setting where hemodynamic variables are frequently monitored to capture changes in sensitivity to PE response due to co-medications. The most practical practice is to administer PE as a bolus or as a continuous intravenous infusion titrated to a target response.

2.4.2 Drugs increasing PE pressor effect – may need to decrease PE dose

A number of drugs from multiple classes appear to enhance the pressor response to PE (Table 18). Specific examples of drugs are provided in this section but it should not be considered an exhaustive list.

Table 18: Drugs may increase phenylephrine pressor response

Class	Drug	Design	Anesthesia	Hemodynamic pressor	Results	**PE dose**
Alpha-adrenergic Agonists	Clonidine Tanaka and Nishikawa (1995)	ASA I or II patients; Clonidine 5 μg/kg; 20 mg famotidine (control- famotidine alone) Clonidine PO dosing prior to thiamylal.	General anesth.- thiamylal. Anesth. maintained- 1% end-tidal enflurane and 67% nitrous oxide in oxygen	Noradrenaline 0.5 μg/kg or 2 μg/kg PE	Clonidine group: 1) greater mean max inc in MAP from the baseline value (21 vs 14 mm Hg, $P < 0.05$); 2) inc the duration of the elevated MAP (7.6 vs 5.1 min, $P < 0.01$).	**Lower doses of PE might be required.**
Oxytocic	Oxytocin Dyer et al. (2009)	a postpartum period substudy, to evaluated the ability of PE to counteract oxytocin induced hypotension postpartum	spinal anesthesia; bupivacaine (10 mg) plus 10 μg of fentanyl administered over 20 sec at the L3/4 interspace	2.5 IU of oxytocin or 2.5 IU of oxytocin mixed with 80 μg PE over a period of 30s starting at 30 s postpartum	PE + oxytocin- MAP was increased ~40% from baseline; oxytocin alone- MAP was decreased 50% from baseline	**Lower doses of PE might be required.**
	Oxytocin Allen et al. (2010)	elective cesarean delivery; placebo or prophylactic PE infusion	Spinal anesthesia; fentanyl 15 μg, preservative-free morphine 150 μg, and 0.75% hyperbaric bupivacaine 1.6 mL.	5 U oxytocin as an i.v. bolus postpartum, followed by an inf. of 25 U in 1 L lactated Ringer soln given over the next 2 h. PE inf. of 25, 50, 75, or 100 μg/min immediately after spinal anesthesia and continued for an additional 10 min postpartum.	showing a reduction in post-delivery hypotension in PE/oxytocin group – oxytocin-alone had 45% hypotensive episodes; oxytocin/PE- 5-25% hypotensive episodes	**Decrease in number of hypotensive episodes with PE co-administration.**
Anesthetic Agents	Ethrane/fentanyl, fentanyl; sufentanil; isoflurane; Schwinn and Reves (1989)	elective coronary artery surgery	Ethrane/fentanyl, fentanyl; sufentanil, and isoflurane; Individual doses are not stated;	Bolus doses of PE (50, 100, 150, 200 μg)	**Use of PE with all anesthetics was associated with larger changes in MAP than anesthetics alone;** **No ind anesthetic agent MAP values was presented; the magnitude of each agent cannot be concluded**	**Data inconclusive.**
Monoamine Oxidase Inhibitors	15 mg phenelzine 3x/day 7 days; 10 mg tranylcypromine 3x/day for 7 days Boakes et al. (1973)	Healthy subjects; terminate infusion when the systolic BP exceeded 170 mm Hg or when the heart rate inc by 40 beats/min or when the subject requested.	-	PE, noradrenaline, adrenaline, and isoprenaline; PE infusions were started at 50 μg/min and increased at 5 min intervals in a logarithmic fashion (100, 200, 400 μg/min, etc.).	PE's vasopressor activity inc 2-3-fold by MOIs; MO is the primary route of PE metabolism; inhibition of this enzyme could increase systemic PE exposure;	**Lower doses of PE might be required.**
Tricyclic Antidepressants	25 mg imipramine 3x/day for 5 days Boakes et al. (1973)		-	PE, noradrenaline, adrenaline, and isoprenaline; PE infusions were started at 50 μg/min and increased at 5 min intervals in a logarithmic fashion (100, 200, 400 μg/min, etc.).	PE's vasopressor activity inc 2-3-fold by imipramine; Tricyclic antidepressants may also potentiate PE's vasopressor activity;	**Lower doses of PE might be required.**
Angiotensin	Aldosterone Aldosterone (500 ng/min) and placebo into brachial artery for 8 min. Schmidt et al. (2003)	Healthy volunteers R, PC, DB, x-over study to study effects of aldosterone in cardiovascular disease; Forearm blood flow measure; Aldo causing hypertension	-	1) acetylcholine at sequential doses of 3, 12, 24, and 48 μg/min; 2) L-NMMA at sequential doses of 2, 4, 8, and 16 μmol/min; (3) sodium nitroprusside at sequential doses of 1.6, 3.2, 6.4, and 12.8 μg/min; and (4) PE at sequential doses of 2.5, 5, 10, and 20 μg/min.	An exaggerated peripheral vasoconstriction was seen with PE 5-20 μg/min **Copyright Material Withheld**	**Lower doses of PE might be required.**

ASA: American Society of Anesthesiology (classification) I-normal healthy pt; II-mild systemic disease; no functional limitation; MAP: mean arterial pressure

2.4.3 Drugs decreasing PE pressor effect – may need to increase PE dose

A number of antihypertensive agents from multiple classes appear to attenuate the pressor response to PE (Table 19). Specific examples of drugs are provided in this section but it should not be considered an exhaustive list.

Table 19: Drugs may decrease phenylephrine pressor response

Class	Drug	Design	Anesthesia	Hemodynamic pressor	Results	**PE dose**
Alpha adrenergic antagonists	Doxazosin Elliott et al. (1982)	Healthy subj.; intravenous administration of doxazosin (12 µg/kg); placebo	-	At 2.25 and 3.25 h post doxazosin dosing, both PE (dose range 0.5-10.0 µg/kg/min) or noradrenaline (dose range 0.02-1.0 µg/kg/min).	Response curve shifted to right; 3-fold PE the dose required to raise MAP by 20 mmHg with co-admin of doxazosin **Doxazosin (solid** and **Placebo (open symbols)** COPYRIGHT MATERIAL WITHHELD	**Higher doses of PE might be required.**
Phosphodiesterase Type 5 (PDE 5) inhibitors	Sildenafil 50 mg (enhances Nitric oxide (NO)-mediated vasodilation) Dishy et al. (2001)	Healthy subj.; (dorsal hand vein constriction) by measuring vein diameter ; Sildenafil 50 mg PO; placebo	-	PE administered as inc doses 12 – 12000 ng/min until a max stable venocontriction	Sildenafil dec the max vasoconstriction induced by PE from 81% ± 3% to 74% ± 3% (p = 0.025).	**(Slightly) Higher doses of PE might be required.**
Adrenergic receptor antagonists	Labetalol (mixed α/β adrenergic receptor antagonist) (dec BP for hypertention treatment) Mehta and Cohn (1977)	Hypertensive subj.; Effects of labetalol 50, 100, 200, 300, and 400 mg Q6h in	-	PE infusion in graded doses starting with 0.02 mg/min which was increased by 0.01 mg/min at 5 minute intervals until diastolic pressure rose by 15 mm Hg.	Response curve shifted to right; 2-fold PE dose probably required for the same effect (control-mean 0.11 mg/min PE; labetalol-mean 0.2 mg/min PE) to raise MAP by 15 mmHg with co-administration of labetalol COPYRIGHT MATERIAL WITHHELD	**Higher doses of PE might be required.**
Calcium channel blockers	Nifedipine; Assess the chronic effect of nifedipine on responsiveness (forearm blood flow) to endothelin-1 and PE vasopressor effects in hypertensive subjects. Sudano et al. (2007)	Hypertensive subj. ; Blood pressure response to Nifedipine 30 – 60 mg/day for 20 weeks.	-	endothelin-1 (potent vasoconstrictor) 0.5, 25, and 50 µg/100 mL of forearm tissue per min for 5 min each dose); PE infusions (0.03, 0.1, 0.3 and 1 µg/100 mL of forearm tissue per min for 5 min)	In hypertensive patients, a chronic Nifedipine dosing reduces the vasoconstriction induced by PE; 2-fold PE dose probably needed for the same effect. COPYRIGHT MATERIAL WITHHELD	**Higher doses of PE might be required**

Benzodiazepines	midazolam (0.05 mg/kg or 0.1 mg/kg); lorazepam (0.05 mg/kg or 0.1 mg/kg) Placebo McNulty et al. (1994)	Hypertensive subj.; Effect of benzodiazepines admin during coronary bypass surgery after cardioplegia on pressor response to PE	Induced with fentanyl 35-50 µg/kg and pancuronium 0.1 mg/kg. Maintained anesthesia with fentanyl, 100 µg/kg, administered in divided doses up to the start of cardiopulmonary bypass;	PE dose needed to maintain the MAP at >50 mm Hg	Mida high and Lora high required inc quantities of PE administered to maintain the MAP at >50 mm Hg (~420 -460 µg PE/Mida or Lora vs. 180 µg PE/ placebo) after rewarming and removal of the aortic crossclamp ($P < 0.03$); 2-fold PE dose probably needed for the same effect. **Quantity of PE Required to Maintain MAP >50 mm Hg** COPYRIGHT MATERIAL WITHHELD	**Higher doses of PE might be required**
Angiotensin converting enzyme (ACE) inhibitors	lipophilic ACEI, quinapril; hydrophilic ACEI, enalapril Placebo Kimura et al. (1998)	Healthy subj.; Evaluate the effects of quinapril (10 mg), and, enalapril (10 mg) on PE vascular response (dorsal hand vein model). (ACEI may act as a vasodilator by reducing using the dorsal hand vein compliance technique. In a the angiotensin II concentration)	-	PE infused cumulatively 40, 78, 156, 313, 620, 1250, 2500, 5000 and 10000 ng/min for 7 min.	ACEIs shifted the PE curve to the right-raising the median PE effective dose; placebo PE ED50 of 189.3 ng/min (square symbols); quinapril inc in ED50 to 481.1 ng/min (circles) stat sig); enalapril inc in ED50 to 266.8 ng/min (not stat sig (triangles)). Significant PE is needed to achieve similar constriction of dorsal hand vein. COPYRIGHT MATERIAL WITHHELD	**Higher doses of PE might be required**

MAP: mean arterial pressure; ED50: half the maximal response in Emax model;

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

Atropine:

Atropine is a competitive antagonist of the muscarinic acetylcholine receptors (acetylcholine being the main neurotransmitter used by the parasympathetic nervous system). Atropine is a parenteral anticholinergic agent and muscarinic antagonist. Atropine increases heart rate. Lower doses of PE might be required.

Steroids

Steroids may enhance sensitivity to pressor response of PE as they sensitize blood vessels to angiotensin and catecholamines. Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions. Lower doses of PE might be required.

Norepinephrine transporter inhibitors: atomoxetine

Norepinephrine is similar to adrenaline. It constricts the blood vessels, increasing blood pressure and blood glucose (sugar) levels. Norepinephrine is used to treat hypotension that can occur with certain medical conditions or surgical procedures. Lower doses of PE might be required.

Methylergonovine maleate (Ergot alkaloids)

Methergine (methylergonovine maleate) belongs to oxytocic class, which directly stimulates vascular smooth-muscle contractions in uterus and cervix and decreases bleeding after delivery. Lower doses of PE might be required.

Centrally-acting sympatholytic agents

Reserpine

A review of the literature revealed that reserpine has also been reported to affect PE pharmacokinetics through inhibition of the vesicular monoamine transporter (Eger and Hamilton 1959).

The sedative and tranquilizing properties of Reserpine are thought to be related to depletion of catecholamines and 5-hydroxytryptamine from the brain. The depression of sympathetic nerve function results in a decreased heart rate and a lowering of arterial blood pressure. Reserpine is used to treat high blood pressure. Reserpine is in a rauwolfia alkaloids class. It works by slowing the activity of the nervous system, causing the heartbeat to slow and the blood vessels to relax. Higher doses of PE might be required.

Guanfacine

Guanfacine hydrochloride is a centrally acting antihypertensive with α2-adrenoceptor agonist. By stimulating these receptors, Guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate (decrease in blood pressure observed after single-dose or long-term oral treatment with Guanfacine). Guanfacine hydrochloride tablets are indicated in the management of hypertension Higher doses of PE might be required.

2.5. General Biopharmaceutics – Not applicable

2.6. Analytical Section

2.4.3 How are PE and its metabolites measured in plasma?

Generally, the bioanalytical methods are not well described or limited in the literature. Hengstmann et al. 1975 and 1982, utilized column chromatography (free amine extraction by solvent extraction) and thin-layer chromatography to measure the radioactivity in order to study the PK of 3H-PE administered either intravenously or orally. The recovery of 3H-PE added to blank sera was 96 ± 0.6% (n=8). Ibrahim et al. (1983) identified PE metabolites that appear in urine after oral or inhalation administration of PE using gas chromatography-mass spectrometry-selected ion monitoring (Hewlett-Packard model 5992A using a silanized glass column (1.8 m x 2 mm i.d.) packed with 5% OV-101 on Chromosorb GHP 100/120 mesh (Supelco)); the gas chromatography was operated isothermally at 180°C for the glycols and acids and at 220°C for the amines; helium was the carrier gas; column effluent was diverted from the ion source for the first 1.5 minutes.

7 **3 Detailed Labeling Recommendations**

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

4.2 Literature references

Eger EI 2nd, Hamilton WK. 1959. The effect of reserpine on the action of various vasopressors. Anthesiology. 20:641-645.

Thiele RH, Nemergut EC, Lynch C. 2011a. The physiologic implications of isolated alpha1 adrenergic stimulation. Anesth Analg. 113(2):284-296.

Thiele RH, Nemergut EC, Lynch C. 2011b. The clinical implications of isolated alpha1 adrenergic stimulation. Anesth Analg. 113(2):297-304.

Schmidt BM, Oehmer S, Delles C, Bratke R, Schneider MP, Klingbeil A, Fleischmann EH, Schmieder RE. 2003. Rapid nongenomic effects of aldosterone on human forearm vasculature. Hypertension. 42(2):156-60.

Schwinn DA, Reves JG. 1989. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg. 68(5):571-578.

Sudano I, Virdis A, Taddei S, Spieker L, Corti R, Noll G, Salvetti A, Luscher TF. 2007. Chronic treatment with long-acting nifedipine reduces vasoconstriction to endothelin-1 in essential hypertension. Hypertension. 49(2):285-290.

Cooper BE. 2008. Review and update on inotropes and vasopressors. AACN Adv Crit Care. 19(1):5-13

George RB, McKeen D, Columb MO, Habib AS. 2010. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing Cesarean delivery. Anesth Analg. 110(1):154-158.

Butterworth JF, Strickland RA, Mark LJ, Kon ND, Zaloga GP. 1990. Calcium does not augment phenylephrine's hypertensive effects. Crit Care Med. 18(6): 603-606.

Martinsson A, Bevegård S, Hjemdahl P. 1986. Analysis of phenylephrine in plasma: initial data about the concentration-effect relationship. Eur J Clin Pharmacol. 30:427-431.

Goertz AW, Schmidt M, Seefelder C, Lindner KH, Georgieff M. 1993a. The effect of phenylephrine bolus administration on left ventricular function during isoflurane-induced hypotension. Anesth Analg. 77:227-231.

Goertz AW, Lindner KH, Seefelder, C, Schirmer U, Beyer M, Georgieff M. 1993b. Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. Anesthesiology. 78: 834-841.

Dyer RA, Piercy JL, Reed AR, Lombard CJ, Schoeman LK, James MF. 2008. Hemodynamic changes associated with spinal anesthesia for cesarean delivery in severe preeclampsia. Anesthesiology. 108:802-811.

Ishiyama T, Oguchi T, Iijima T, Matsukawa T, Kashimoto S, Kumazawa T. 2003. Ephedrine, but not phenylephrine, increases bispectral index values during combined general and epidural anesthesia. Anesth Analg. 97:780-784.

Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, Greenwood J, James MF. 2009. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology. 111(4):753-765.

Alahuhta S, Räsänen J, Jouppila P, Jouppila R, Hollmén AI. 1992. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section. Int J Obstet Anesth 1:129-134.

Nygren A, Thorén A, Ricksten SE. 2006. Vasopressors and intestinal mucosal perfusion after cardiac surgery: norepinephrine vs phenylephrine. Crit Care Med. 34:722-729.

Brooker RF, Butterworth JF, Kitzman DW, Berman JM, Kashtan HI, McKinley AC. 1997. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia a randomized, doubleblind, cross-over comparison of phenylephrine and epinephrine. Anesthesiology. 86:797- 805.

Hardman JG, Limbird LE, Eds. 2001. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York, NY: McGraw-Hill, p.1994.

Johnston WE, Dewitt DS, Vinten-Johansen J, Stump DA, Prough DS. 1994. Phenylephrine does not reduce cerebral perfusion during canine cardiopulmonary bypass. Anesth Analg. 79:14-18.

Meyer SM, Fraunfelder FT. 1980. 3. Phenylephrine hydrochloride. Ophthalmology. 87(11):1177-1180.

Ibrahim KE, Midgley JM, Crowley JR, Williams CM. 1983. The mammaliam metabolism of R-(-)-*m*-synephrine. J Pharm Pharmacol. 35:144-147.

Schering-Plough Corporation. 2007. Understanding phenylephrine metabolism, pharmacokinetics, bioavailability and activity. Submitted to the Nonprescription Drugs Advisory Committee. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-01-Schering-Plough.pdf.

White M, Fourney A, Mikes E, Leenen FH. 1999. Effects of age and hypertension on cardiac responses to the alpha1-agonist phenylephrine in humans. Am J Hypertens. 12(2 Pt 1):151-158.

Stein CM, Lang CC, Singh I, He HB, Wood AJJ. 2000. Increased vascular adrenergic vasoconstriction and decreased vasodilation in blacks additive mechanisms leading to enhanced vascular reactivity. Hypertension. 36:945-951.

Wolzt M, Schmetterer L, Rheinberger A, Salomon A, Unfried C, Breiteneder H, Ehringer H, Eichler HG, Fercher AF. 1995. Comparison of non-invasive methods for the assessment of haemodynamic drug effects in healthy male and female volunteers: sex differences in cardiovascular responsiveness. Br J Clin Pharmacol. 39(4):347-359.

Grassi G, Seravalle G, Dell'Oro R, Turri C, Bolla GB, Mancia G. 2000. Adrenergic and reflex abnormalities in obesity-related hypertension. Hypertension. 36(4):538-542.

MacGilchrist AJ, Sumner D, Reid JL. 1991. Impaired pressor reactivity in cirrhosis: evidence for a peripheral vascular defect. Hepatology. 13(4):689-694.

Abiose AK, Aronow WS, Moreno H, Nair CK, Blaschke TF, Hoffman BB. 2007. Increased vascular α 1-adrenergic sensitivity in patients with renal failure. Am J Ther. 14(5):427-434.

Strieper MJ, Campbell RM. 1993. Efficacy of alpha-adrenergic agonist therapy for prevention of pediatric neurocardiogenic syncope. J Am Coll Cardiol. 22(2):594-597.

Mehta J, Cohn, JN. 1977. Hemodynamic Effects of Labetalol, an Alpha and Beta Adrenergic Blocking Agent, in Hypertensive Subjects. Circulation. Vol. 55(2): 370-375.

Tanaka M, Nishikawa T. 1995. Effects of clonidine premedication on the pressor response to α-adrenergic agonists. Br. J. Anaesth. 75:593-597.

Allen TK, George RB, White WD, Muir HA, Habib AS. 2010. A double-blind, placebo controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for Cesarean delivery. Anesth Analg. 111:1221-1229.

Boakes AJ, Laurence DR, Teoh PC, Barar FS, Benedikter LT, Prichard BN. 1973. Interactions between sympathomimetic amines and antidepressant agents in man. Br Med J. 1(5849):311-315.

Elliott HL, Meredith PA, Sumner DJ, McLean K, Reid JL. 1982. A pharmacodynamic and pharmacokinetic assessment of a new alpha-adrenoceptor antagonist, doxazosin (UK33274) in normotensive subjects. Br J Clin Pharmacol. 13(5):699-703.

Dishy V, Sofowora G, Harris PA, Kandcer M, Zhan F, Wood AJ, Stein CM. 2001. The effect of sildenafil on nitric oxide-mediated vasodilation in healthy men. Clin Pharmacol Ther. 70(3):270-279.

Sudano I, Virdis A, Taddei S, Spieker L, Corti R, Noll G, Salvetti A, Luscher TF. 2007. Chronic treatment with long-acting nifedipine reduces vasoconstriction to endothelin-1 in essential hypertension. Hypertension. 49(2):285-290.

McNulty SE, Gratch D, Kim JY. 1994. Comparative vascular effects of midazolam and lorazepam administered during cardiopulmonary bypass. Anesth Analg. 79(4):675-680.

Kimura M, Umemura K, Kosuge K, Nishimoto M, Ohashi K, Nakashima M. 1998. Attenuation by ACE inhibitor drugs of alpha-adrenoceptor sensitivity in human vessels: possible differences related to drug lipophilicity. Br J Clin Pharmacol. 46(6):599-603.

4.3 Consult Review (including Pharmacometric Reivews) – Not Applicable

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**204300**	**Brand Name**	**Phenylephrine HCl Injection**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**-**
Medical Division	**DAAAP**	**Drug Class**	**Non-depolarizing neuromuscular blocking agent**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Treatment (b) (4) of hypotension during anesthesia**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Injection 1%, 10 mg/mL**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**Intravenous bolus or infusion titrated to effect**
Date of Submission	**2/8/13**	**Route of Administration**	**Intravenous injection**
Estimated Due Date of OCP Review	***10/8/13***	**Sponsor**	**Éclat Pharmaceuticals**
Medical Division Due Date	***11/8/13***	**Priority Classification**	**Standard**
PDUFA Due Date	***12/8/13***		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			

Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

Note: No clinical studies were conducted with the proposed product. This NDA relies on literature information.

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			This will be assessed
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Literature information provided
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	Literature information provided
5	Has a rationale for dose selection been submitted?	x			Literature information provided
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			Literature information provided

12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	This will be assessed
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			This will be assessed
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			This will be assessed
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	The applicant submitted literature information
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			This will be assessed
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___
If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Éclat Pharmaceuticals submitted a New Drug Application (NDA) for phenylephrine HCl Injection 1% (10 mg/mL), USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The proposed indication is for the treatment (b) (4) of hypotension during anesthesia. The approval of this NDA submission is based on the literature in adult population. The Applicant intends to rely solely on literature to support the non-clinical, clinical pharmacology, clinical safety and efficacy of the proposed phenylephrine HCl injection. Safety and effectiveness in pediatric patients have not been established; no studies were identified that evaluated the use of phenylephrine for the sought after indication. It is noted that the Applicant appears not to submit any pediatric plan.

Phenylephrine is a selective α-adrenergic agonist that causes prominent vasoconstriction, resulting in an increase in blood pressure. Phenylephrine HCl injection, USP, is intended for intravenous administration, and, has been marketed unapproved for many years. Recently, phenylephrine HCl Injection for intravenous use (N203826) was approved on 12/20/12 indicated for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.

An End-of-Phase 2 meeting was held with the Applicant on October 29th, 2012, to discuss the appropriateness of literature information to support approval. The Agency conveyed to the Applicant that an NDA submission and a request for a biowaiver can be based on the appropriate literature if the formulations used in the literature are appropriate for reference. In this submission the Applicant submitted literature information for the approval. However, it is noted that there is no formal biowaiver request. The referenced literature in the submission included studies with phenylephrine intravenous injections, which appear to address including, but not limited to, Pharmacokinetics following intravenous administration in healthy subjects, Mass balance and metabolism, Pharmacodynamics -- vasoconstrictive effects (including but not limited to, pediatric, race, elderly, hypertensive, low cardiac output, hepatic and renal impairments, etc.), Drug interactions (including, but not limited to, pharmacodynamic effects with α adrenergic agonists and antagonists, MAOs, angiotensin-converting enzyme inhibitors, etc.), Cardiac safety (QT prolongation), etc.

From a clinical pharmacology perspective, the adequacy of the literature information in the application for the product labeling purpose will be a review issue. The application is recommended for filing, and, there are no comments/information requests to be conveyed to the Applicant at this time.

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

/s/

DAVID J LEE
03/20/2014

YUN XU
03/20/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

MEMO to New Drug Application Filing Form Office of Clinical Pharmacology			
General Information About the **Resubmission**			
	Information		**Information**
NDA/BLA Number	**204300**	**Brand Name**	**Phenylephrine HCl Injection**
OCP Division	**II**	**Generic Name**	**-**
Medical Division	**DAAAP**	**Drug Class**	**Non-depolarizing neuromuscular blocking agent**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Treatment (b) (4) of hypotension during anesthesia**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Injection 1%, 10 mg/mL**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**Intravenous bolus or infusion titrated to effect**
Date of Submission	**6/28/13**	**Route of Administration**	**Intravenous injection**
Estimated Due Date of OCP Review	***3/6/14***	**Sponsor**	**Éclat Pharmaceuticals**
Medical Division Due Date	***3/20/14***	**Priority Classification**	**505(b)(2)**
PDUFA Due Date	***4/28/14***		

Éclat Pharmaceuticals re-submitted a New Drug Application (NDA) for phenylephrine HCl Injection 1% (10 mg/mL), USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The Agency issued a Refuse to File letter to the Applicant on 4/5/13 (deficiencies in construct of Integrated Summary of Efficacy and Integrated Summary of Safety).

The proposed indication is for the treatment (b) (4) of hypotension during anesthesia. The approval of this NDA submission is based on the literature in adult population. The Applicant intends to rely solely on literature to support the non-clinical, clinical pharmacology, clinical safety and efficacy of the proposed phenylephrine HCl injection. Safety and effectiveness in pediatric patients have not been established; no studies were identified that evaluated the use of phenylephrine for the sought after indication. It is noted that the Applicant appears not to submit any pediatric plan.

From a clinical pharmacology perspective, the adequacy of the literature information in the application for the product labeling purpose will be a review issue. The application is recommended for filing, as previously stated (initial NDA Filing Memo dated 3/28/13), and, there are no comments/information requests to be conveyed to the Applicant at this time.

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

/s/

DAVID J LEE
08/26/2013

YUN XU
08/26/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204300
Submission Date	6/28/13 - resubmission
Product name, generic name of the active	Phenylephrine HCl Injection
Dosage form and strength	Solution for Injection – 1% (10 mg per mL)
Route of Administration	IV bolus or infusion
Applicant	Eclat Pharmaceuticals
Clinical Division	Division of Anesthesia and Analgesia Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?		x	A BA/BE waiver request is not included in this submission. However, a biowaiver is not applicable for this product. The Applicant relies on published literature to support the safety, efficacy and PK of the proposed drug product. The published information/data will be evaluated by the Clinical and ClinPharm Reviewers.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	

8.	Is information on mixing the product with foods or liquids included?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
9.	Is there any in *vivo* BA or BE information in the submission?	x		This is a literature based NDA. The PK information included in the published references will be evaluated by the Office of Clinical Pharmacology.
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
12.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY:

The original NDA was refused to file (RTF) due to clinical issues. The Applicant has resubmitted this NDA on 6/28/13. The resubmission is identical to the original NDA submission from Biopharmaceutics perspective. The proposed drug product is a sterile solution of 1% phenylephrine hydrochloride, USP in water for injection. It can be administered intravenously either as a bolus or in a diluted solution as a continuous infusion. The proposed drug product is a currently marketed unapproved drug product. The proposed indication is for the treatment (b) (4) of hypotension during anesthesia.

Currently, there are three companies that market unapproved phenylephrine hydrochloride injection, USP: West-Ward (previously Baxter), Sandoz and American Regent. Teva previously manufactured the product, but has since discontinued production. The table below provides a comparison between Éclat's proposed formulation and the previously and currently marketed formulations of phenylephrine hydrochloride injection, USP. Shown are amounts per mL.

(b) (4)

This NDA contains published literature references in lieu of clinical studies. The Applicant is relying on published literature for efficacy, safety and PK information. The proposed formulation is (b) (4) to the West-Ward formula, (b) (4) to the Sandoz, American Regent and Winthrop formulas. (b) (4)

Each formulation complies with

the USP monograph for phenylephrine HCl Injection, USP. The vast majority of the published clinical pharmacology, efficacy and safety studies included in support of this NDA do not identify the manufacturer or the trade name of the phenylephrine drug product used in the study. The only studies that identified the trade name or supplier of the phenylephrine are:

- Schmidt et al. (2003): Neo-Synephrine, Abbott Laboratories
- Schwinn and Reves (1989): Winthrop Laboratories, New York, NY
- Sudano et al. (2007): Farmigea (S.p.A)

Based on information regarding the eventual acquisition of Winthrop Laboratories by Abbott Laboratories, (b) (4) . The Applicant was unable to identify the formulation of the test drug manufactured by Farmigea. The Applicant believes that (b) (4) it is appropriate to rely on these studies as evidence of safety and efficacy of the proposed product. The minor differences in the formulations are not expected to have an effect on bioavailability, safety, efficacy or pharmacokinetics of this parenteral drug product intended for intravenous administration. Therefore, Éclat has not conducted any original Biopharmaceutics or clinical pharmacology studies in support of this NDA and is relying on published literature for that information.

CONCLUSION:

The differences between the drug product formulations used in the published PK studies and the proposed drug product formulation are minor and are not expected to change the bioavailability of the drug administered by intravenous bolus injection or infusion. The Applicant has established a bridge between the clinical data presented in the literature and the proposed formulation. The evaluation and acceptability of the human PK data from the literature will be determined by the Clinical Pharmacology Reviewer from OCP.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 204300 is fileable. However, this NDA does not require further assessment by the ONDQA-Biopharmaceutics team.

{See appended electronic signature page} *8/26/13*
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page} *8/26/13*
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
08/26/2013

ANGELICA DORANTES
08/26/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**204300**	**Brand Name**	**Phenylephrine HCl Injection**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**-**
Medical Division	**DAAAP**	**Drug Class**	**Non-depolarizing neuromuscular blocking agent**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Treatment (b) (4) of hypotension during anesthesia**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Injection 1%, 10 mg/mL**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**Intravenous bolus or infusion titrated to effect**
Date of Submission	**2/8/13**	**Route of Administration**	**Intravenous injection**
Estimated Due Date of OCP Review	***10/8/13***	**Sponsor**	**Éclat Pharmaceuticals**
Medical Division Due Date	***11/8/13***	**Priority Classification**	**Standard**
PDUFA Due Date	***12/8/13***		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

Note: No clinical studies were conducted with the proposed product. This NDA relies on literature information.

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			This will be assessed
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Literature information provided
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	Literature information provided
5	Has a rationale for dose selection been submitted?	x			Literature information provided
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			Literature information provided
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	This will be assessed
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			This will be assessed
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			This will be assessed
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	The applicant submitted literature information
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			This will be assessed
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Éclat Pharmaceuticals submitted a New Drug Application (NDA) for phenylephrine HCl Injection 1% (10 mg/mL), USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The proposed indication is for the treatment (b) (4) of hypotension during anesthesia. The approval of this NDA submission is based on the literature in adult population. The Applicant intends to rely solely on literature to support the non-clinical, clinical pharmacology, clinical safety and efficacy of the proposed phenylephrine HCl injection. Safety and effectiveness in pediatric patients have not been established; no studies were identified that evaluated the use of phenylephrine for the sought after indication. It is noted that the Applicant appears not to submit any pediatric plan.

Phenylephrine is a selective α-adrenergic agonist that causes prominent vasoconstriction, resulting in an increase in blood pressure. Phenylephrine HCl injection, USP, is intended for intravenous administration, and, has been marketed unapproved for many years. Recently, phenylephrine HCl Injection for intravenous use (N203826) was approved on 12/20/12 indicated for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.

An End-of-Phase 2 meeting was held with the Applicant on October 29th, 2012, to discuss the appropriateness of literature information to support approval. The Agency conveyed to the Applicant that an NDA submission and a request for a biowaiver can be based on the appropriate literature if the formulations used in the literature are appropriate for reference. In this submission the Applicant submitted literature information for the approval. However, it is noted that there is no formal biowaiver request. The referenced literature in the submission included studies with phenylephrine intravenous injections, which appear to address including, but not limited to, Pharmacokinetics following intravenous administration in healthy subjects, Mass balance and metabolism, Pharmacodynamics -- vasoconstrictive effects (including but not limited to, pediatric, race, elderly, hypertensive, low cardiac output, hepatic and renal impairments, etc.), Drug interactions (including, but not limited to, pharmacodynamic effects with α adrenergic agonists and antagonists, MAOs, angiotensin-converting enzyme inhibitors, etc.), Cardiac safety (QT prolongation), etc.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

From a clinical pharmacology perspective, the adequacy of the literature information in the application for the product labeling purpose will be a review issue. The application is recommended for filing, and, there are no comments/information requests to be conveyed to the Applicant at this time.

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

/s/

DAVID J LEE
03/28/2013

YUN XU
03/28/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204300
Submission Date	2/8/13
Product name, generic name of the active	Phenylephrine HCl Injection
Dosage form and strength	Solution for Injection – 1% (10 mg per mL)
Route of Administration	IV bolus or infusion
Applicant	Eclat Pharmaceuticals
Clinical Division	Division of Anesthesia and Analgesia Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?		x	A BA/BE waiver request is not included in this submission. However, a biowaiver is not applicable for this product. The Applicant relies on published literature to support the safety, efficacy and PK of the proposed drug product. The published information/data will be evaluated by the Clinical and ClinPharm Reviewers.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	

8.	Is information on mixing the product with foods or liquids included?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
9.	Is there any in *vivo* BA or BE information in the submission?	x		This is a literature based NDA. The PK information included in the published references will be evaluated by the Office of Clinical Pharmacology.
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
12.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY:

The proposed drug product is a sterile solution of 1% phenylephrine hydrochloride, USP in water for injection. It can be administered intravenously either as a bolus or in a diluted solution as a continuous infusion. The proposed drug product is a currently marketed unapproved drug product. The proposed indication is for the treatment (b) (4) of hypotension during anesthesia.

Currently, there are three companies that market 1% phenylephrine hydrochloride injection, USP: West-Ward (previously Baxter), Sandoz and American Regent. West-Ward's drug product was approved on December 20, 2012 (NDA 203826), whereas Sandoz and American Regent are marketing their drug product unapproved. (b) (4) Teva previously manufactured a 1% phenylephrine hydrochloride product, but has since discontinued production. The table below provides a comparison between Éclat's proposed formulation and the previously and currently marketed formulations of phenylephrine hydrochloride injection, USP. Shown are amounts per mL.

(b) (4)

This NDA contains published literature references in lieu of clinical studies. The Applicant claims that this NDA (203400) does not rely on NDA 203826 from West-Ward, but instead this NDA is relying on published literature for efficacy, safety and PK information. (b) (4)

(b) (4)

Each formulation complies with the USP monograph for phenylephrine HCl Injection, USP. The vast majority of the published clinical pharmacology, efficacy and safety studies included in support of this NDA do not identify the manufacturer or the trade name of the phenylephrine drug product used in the study.

The only studies that identified the trade name or supplier of the phenylephrine are:

- Schmidt et al. (2003): Neo-Synephrine, Abbott Laboratories
- Schwinn and Reves (1989): Winthrop Laboratories, New York, NY
- Sudano et al. (2007): Farmigea (S.p.A)

(b) (4)

The Applicant believes that

(b) (4)

it is appropriate to rely on these studies as evidence of safety and efficacy of the proposed product. The minor differences in the formulations are not expected to have an effect on bioavailability, safety, efficacy or pharmacokinetics of this parenteral drug product intended for intravenous administration. Therefore, the Applicant has not conducted any original Biopharmaceutics or clinical pharmacology studies in support of this NDA and is relying on published literature for that information.

CONCLUSION:

The differences between the drug product formulations used in the published PK studies and the proposed drug product formulation are minor and are not expected to change the bioavailability of the drug administered by intravenous bolus injection or infusion. The Applicant has established a bridge between the clinical data presented in the literature and the proposed formulation. The evaluation and acceptability of the human PK data from the literature will be determined by the Clinical Pharmacology Reviewer from OCP.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 204300 is fileable. However, this NDA does not require further assessment by the ONDQA-Biopharmaceutics team.

{See appended electronic signature page} *3/27/13*
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page} *3/27/13*
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

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

/s/

ELSBETH G CHIKHALE
03/27/2013

ANGELICA DORANTES
03/27/2013