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APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA number	203826
Submission type	Standard 505(b)(2)
Submission date	01/12/2012
Applicant name	West-Ward Pharmaceutical Corp.
Proposed brand name	Phenylephrine hydrochloride, USP
Generic name	Phenylephrine hydrochloride
Dosage form	Solution for injection
Dosage strengths	10 mg/mL
Proposed indication	To increase blood pressure in acute hypotensive states
OCP division	Division of Clinical Pharmacology 1
OND division	Cardiovascular and Renal Products
Primary reviewer	Sudharshan Hariharan, Ph.D.
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1. EXECUTIVE SUMMARY

West-Ward Pharmaceutical Corporation is seeking approval of Phenylephrine hydrochloride injection, USP (10 mg/mL, 1 mL vial) via the 505(b)(2) pathway relying on published literature to support the non-clinical profile, clinical pharmacology, clinical safety and efficacy of the proposed drug product. There is no listing of a Reference Listed Drug (RLD) in the Electronic Orange Book for Phenylephrine hydrochloride injection, USP. However, Phenylephrine hydrochloride injection, USP has historically been marketed under the ‘Grandfathered’ exemption in section 201(p)(1) of the Federal Food Drug and Cosmetic Act. A literature based 505(b)(2) submission without a RLD is supported by the Guidance for FDA Staff and Industry, ‘Marketed Unapproved Drugs – Compliance Policy Guide’ Sec. 440.100.

The clinical pharmacology package for this application primarily consists of published literature addressing the following features of phenylephrine – (i) mass balance, (ii) pharmacokinetics, (iii) vasoconstrictive effects, (iv) blood pressure response in healthy subjects, (v) dose-response in target patients, and (vi) impact of intrinsic and extrinsic factors on vasoconstrictive/blood pressure response.

1.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The key clinical pharmacology features of phenylephrine hydrochloride are summarized below:

- When administered intravenously, phenylephrine follows a bi-exponential decline with rapid distribution (α -phase half-life <5 min) from the central compartment to peripheral tissues and end organs.
- Phenylephrine has a rapid onset of blood pressure response (<5 min). The time to offset the drug effect is approx. 10-15 min which is consistent with the initial rapid elimination from the systemic circulation. Maintenance of blood pressure around a target over a prolonged period of time will warrant an infusion regimen.
- There is a dose-dependent increase in the blood pressure response of phenylephrine in healthy subjects. Heart rate decreases (reflex bradycardia) with increase in exposures of phenylephrine.
- There is an increase in blood pressure with intravenous infusion or bolus of phenylephrine in subjects with hypotension due to induction of spinal anesthesia during elective cesarean delivery. However, the pharmacodynamic response to phenylephrine is dependent on the extent of spinal block.
 - Based on the submitted information, a reasonable initial starting dose when phenylephrine is administered in a bolus setting is 100 μ g. Additional rescue boluses might be required depending on the extent of spinal block and the target maintenance of blood pressure. Doses lower than 100 μ g are often associated with higher frequencies of hypotensive episodes requiring more number of PE rescues.

- When administered as a continuous infusion, phenylephrine infusion rates ranging from 12 µg/min to 50 µg/min resulted in fewer hypotensive as well as hypertension/bradycardia episodes.
- Under general anesthesia, phenylephrine caused a dose-dependent increase in mean arterial pressure (MAP) in patients undergoing coronary artery bypass graft (CABG) surgery
- A trend for dose-response of phenylephrine was observed in hypotensive or normotensive patients with sepsis.
 - Based on the available information, an initial infusion rate of 0.5-1.0 µg/kg/min is necessary to elicit a discernible pharmacological response. The target MAP can be achieved by up titration every 30 min. The maximum mean response i.e., change from baseline in MAP, is achieved by a phenylephrine dose of ~6 µg/kg/min. Doses greater than 6 µg/kg/min might not result in significant incremental MAP response.
- Drug interactions with other co-medications primarily affect the pharmacodynamic response of phenylephrine. Specific dosing recommendations to address these interactions are not required because phenylephrine will be used in a controlled clinical setting and titrated to a target response.

1.2. Phase 4 Requirements / Commitments

No Phase 4 Requirements / Commitments are proposed at this point of time.

1.3. Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed published literature supporting clinical pharmacology aspects of NDA 203826 and based on the blood pressure effect recommends approval of phenylephrine hydrochloride. The specific indications for phenylephrine use are addressed in the clinical review.

2. QUESTION BASED REVIEW

The pharmacokinetics and pharmacodynamics of phenylephrine (PE) are known and understood. Clinical pharmacology information presented in this submission is reviewed in this document. From a pharmacodynamic perspective, the document specifically focuses on the blood pressure/MAP response. An abridged version of the question based review is used to address the clinical pharmacology of issues of phenylephrine.

2.1. What are the pharmacokinetic characteristics of PE?

Pharmacokinetic data of PE in human is sparse. There is one publication by Hengstmann and Goronzy studying the pharmacokinetics of PE following an intravenous infusion¹. Tritiated phenylephrine (³H-PE) at a dose of 1 mg was infused for 15 min in 4 healthy volunteers. Following stoppage of infusion, PE exhibited biphasic elimination as observed by an initial rapid distribution followed by relatively slow elimination. The observed mean data was fitted appropriately to a 2-compartment *i.v.* infusion model with first order elimination as shown in Fig. 1. The calculated pharmacokinetic parameters are shown as an inset to Fig. 1. It is seen that PE rapidly distributed to peripheral tissues upon intravenous administration with an average steady state volume of distribution (V_{ss}) of 120 L. The distribution half-life (α -phase) as expected was very short (<5 min) and is the dominant half-life (on an average 80% of PE is eliminated in ~10 min following cessation of the infusion). The terminal elimination half-life (β -phase) was about an hour. The quick onset and offset of action of PE (to be seen in later section) is supported by pharmacokinetics indicating a direct effect of PE. Therefore, when a sustained pharmacological PE response is warranted, an *i.v.* infusion might be better suited than a bolus, as defined by the pharmacokinetics of PE.

In another study by Martinsson *et al*, where PE was administered as step-wise infusions (PE dose range: 0.5 to 4 $\mu\text{g}/\text{kg}/\text{min}$, time of infusion: 6 min) to nine healthy subjects, the concentration of PE increased in a linear fashion with dose². The inter-subject variability (CV%) calculated from this study (n=9) was ~100%.

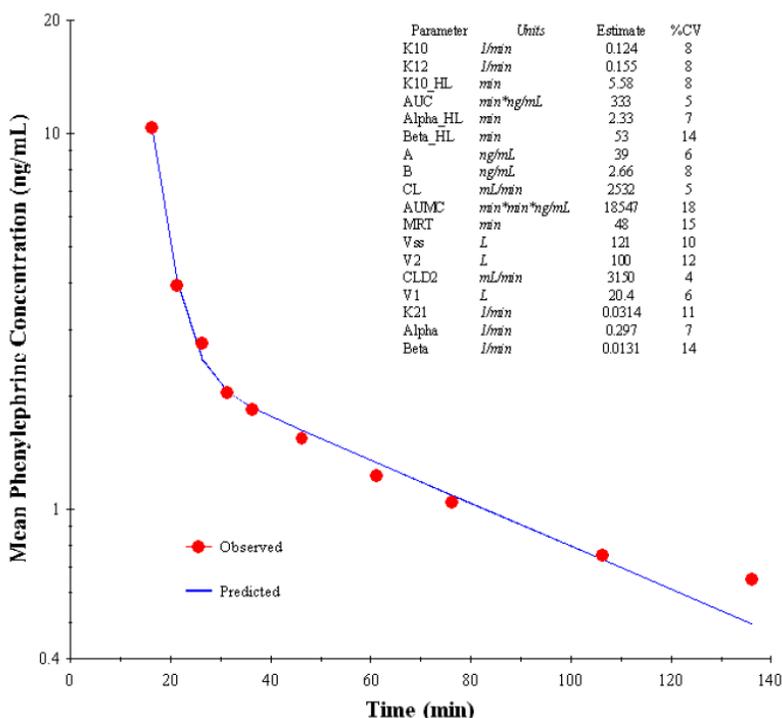


Figure 1: Mean PE plasma concentrations fitted to a 2-compartment model with pharmacokinetic parameters shown in the inset.

Note: PE is administered as a 15 min infusion.

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

Mass balance of PE was studied following 1 mg ³H-PE administered intravenously¹. PE is extensively metabolized by the liver with only 12% of the dose excreted unchanged in the urine. Deamination by monoamino oxidase is the primary metabolic pathway resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57% of PE dose. There are other metabolites which are sulfate and glucuronide conjugated products as shown in Fig. 2, accounting for the remaining radioactivity. Following *i.v.* administration, PE and its metabolites are primarily eliminated in the urine. Eighty six percent of the dose was recovered in the urine in 48 h with the majority (approx. 80%) being eliminated within first 12 h.

PE is the active moiety. When screened for receptor activity, the metabolites were found to be inactive to both α_1 - and α_2 -adrenergic receptors³.

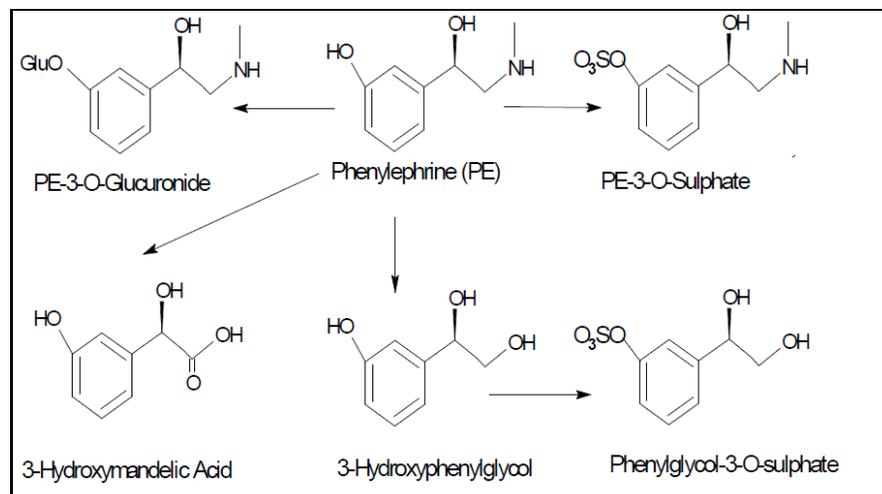


Figure 2: Metabolic profile of PE .
Source: Summary of clinical pharmacology document generated by the sponsor (page 56, Fig. 2.7.2.3-3).

2.3. What is the proposed mechanism of action of PE and the therapeutic indication claimed in this submission?

PE is a selective α_1 -adrenergic receptor agonist which increases mean arterial pressure (MAP) primarily through an increase in systemic vascular resistance. The elevated MAP results in reflex bradycardia (reduction in heart rate) and consequently a decrease in cardiac output.

PE is indicated for increasing blood pressure in acute hypotensive states, such as shock, and in perioperative hypotensive settings such as during surgical procedures under neuraxial anesthesia (e.g., cesarean delivery) or general anesthesia (e.g., CABG surgery).

2.4. What are the vasoconstrictive effects of PE in healthy subjects?

Published literature supports the vasoconstrictive effects of PE in healthy subjects⁴⁻¹¹. In these studies, PE was infused in a step-wise manner with a wide dose-range and the peripheral venous responsiveness to PE was measured by dorsal hand vein technique (DHVT). This method explores the effect of drugs in human vascular bed by monitoring vein size. The technique allows small infusions of drug to study wide dose range and prevents potential confounding systemic effects and reflex alterations. Moreover, peripheral venous responsiveness as measured by DHVT is shown to correlate with systemic vascular responsiveness*. Infusion time ranged from 2 to 10 min across these studies. Table 1 summarizes the list of studies assessing the dose-vasoconstriction response of PE with reported E_{max} and ED_{50} values. The results show that PE reproducibly causes vasoconstriction in a dose-dependent manner; however we observe variability in response with ED_{50} values ranging from 60 to 800 ng/min. A representative mean dose-response curve from a study by Harada *et al*⁷ is shown in Fig. 3.

* Vincent J, Blaschke TF, Hoffman BB. Vascular reactivity to phenylephrine and angiotensin II: comparison of direct venous and systemic vascular responses. Clin Pharmacol Ther. 1992 Jan;51(1):68-75.

Table 1: Summary of studies assessing dose-vasoconstriction response of PE in healthy subjects⁴⁻¹¹

Reference	Phenylephrine Dose Range (ng/min)	Subject Population	E _{max} (%)	ED ₅₀ (ng/min)	ED ₈₀ (ng/min)	logED ₅₀
Vincent	21-6775	12 (7 men, 5 women)	95 ± 11 ^a	227 ^b	—	2.4 ± 0.4 ^a
Harada	32-8192	8 men	107.6 ± 15.8 ^a	573 ± 352 ^a	—	—
Harada	16-8192	9 men	100 ± 5.9 ^a	798 ± 652 ^a	—	—
Harada	16-8192	9 men	101 ± 2.1 ^c	—	—	2.69 ± 0.10 ^c
Abdelmawla	33-10,000	12 men	84.13 ± 8.09 ^c	60.98 ^b	—	1.79 ± 0.10 ^c
Schindler	47-1500	12 men	—	—	391 ± 545 ^a	—
Muszkat	12-12,000	62 (36 men, 26 women)	90.8 (82.2-99.6) ^d	177.8 (40.7-436.5) ^d	—	—
Sofowora	12-12,000	74 (35 men, 39 women)	—	431-513 ^e	—	—

Abbreviations: —, not reported; E_{max}, maximum response; ED₅₀, dose producing half the maximal effect; ED₈₀, dose producing 80% constriction.

^a Value is the mean ± SD.

^b Value is the geometric mean.

^c Value is the mean ± SEM.

^d Value is the median (interquartile range [IQR]).

^e Range in 3 subgroups of patients with different α-adrenergic receptor genotypes.

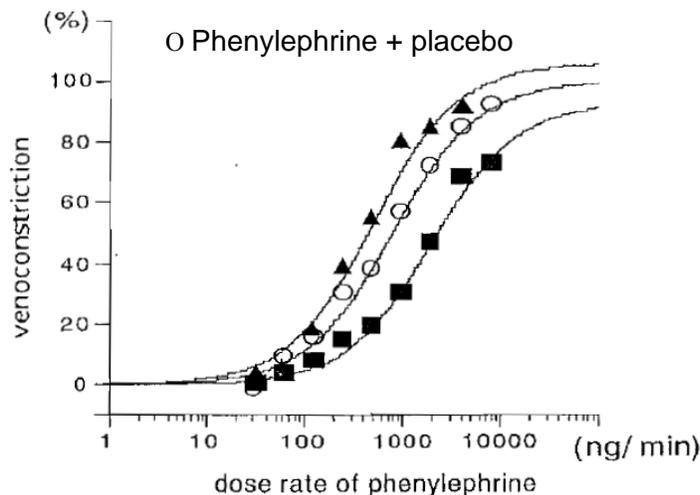


Figure 3: Mean dose-venoconstriction response curve for PE in healthy subjects (o) – Harada *et al*⁷

2.5. What is the effect of PE on hemodynamics in healthy subjects?

The effect of PE on systemic blood pressure in normal, healthy volunteers is described in a number of articles¹²⁻²¹. In majority of the studies, PE was infused in a step-wise manner covering a dose range as low as 30 µg/min to as high as 1500 µg/min. Infusion times were generally short, ranging from 5 to 20 min across these studies. PE was titrated to a target blood pressure response, generally to a change from baseline in SBP of 20 - 30 mmHg. Hemodynamic variables

were monitored frequently so as to allow incremental titration of PE dose to the desired target. It should be noted that the drug effect for any given dose was not washed out before the administration of the next incremental dose.

Based on a naïve-pooled data of the study and dose level means, there was a linear trend for dose-cumulative response relationship (Fig. 4).

On the other hand, there was a cumulative decrease in heart rate with PE infusion across all the studies, supporting the reflex bradycardia effects (Fig. 4). This relation showed a non-linear trend with a maximum mean change from baseline in heart rate tapering off around 20 bpm.

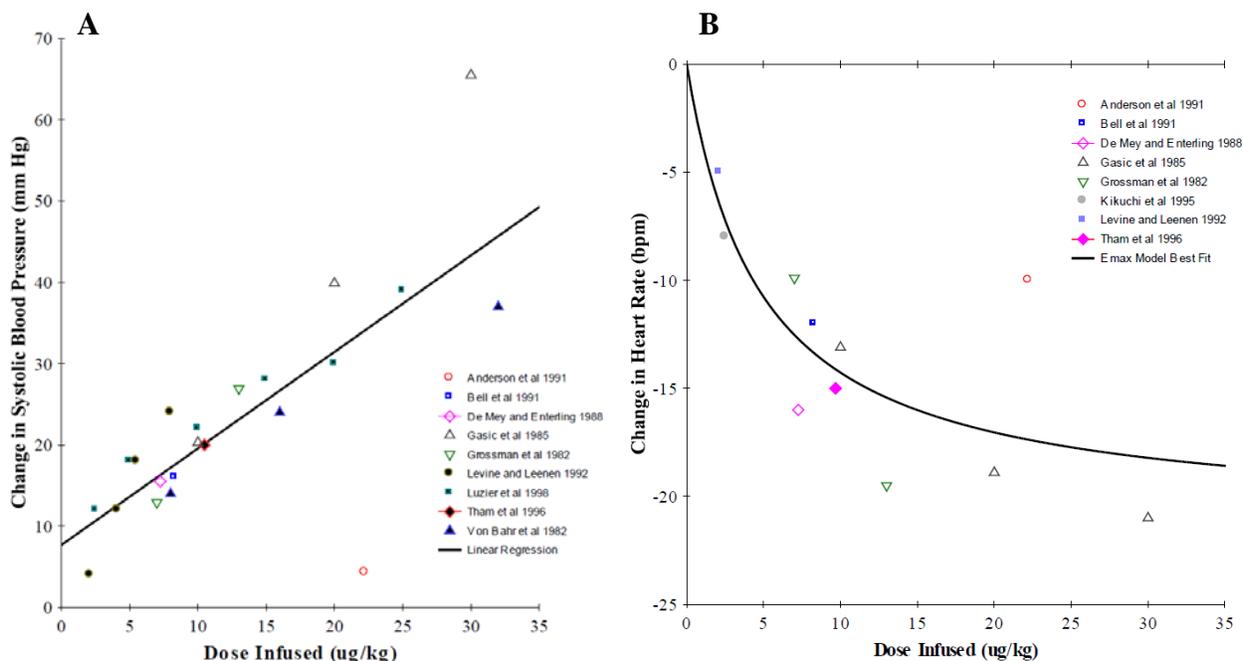


Figure 4: Exposure-blood pressure (A) and -heart rate (B) relationship across data pooled from various healthy subject studies¹²⁻²¹.

2.6. What is the onset and offset of action of PE?

The onset and offset of action (blood pressure and heart rate) as reviewed across many studies is rapid. Time course of PE effect on blood pressure and heart rate is shown in a study by Bell *et al*, where PE was administered as an *i.v.* infusion titrated over the dose range of 30 to 120 $\mu\text{g}/\text{min}$ in order to achieve a target of 20 mmHg in SBP¹³. It is seen from Fig. 5 that the onset of action is immediate with the target blood pressure response of 20 mmHg SBP reached within 20 min. Similarly, upon stopping the infusion, the effects wear out rapidly, as seen by blood pressure values returning to baseline within 10 min, indicating that the pharmacological response is direct and reversible. Also, there is a decrease in the heart rate of PE following a similar onset and offset to that of blood pressure. This is expected as the decrease in heart rate (reflex bradycardia) is in response to the increase in systemic vascular resistance.

Therefore, based on most of the studies reviewed, PE has an onset of action which is immediate (<5 min) and an offset around 10-15 min.

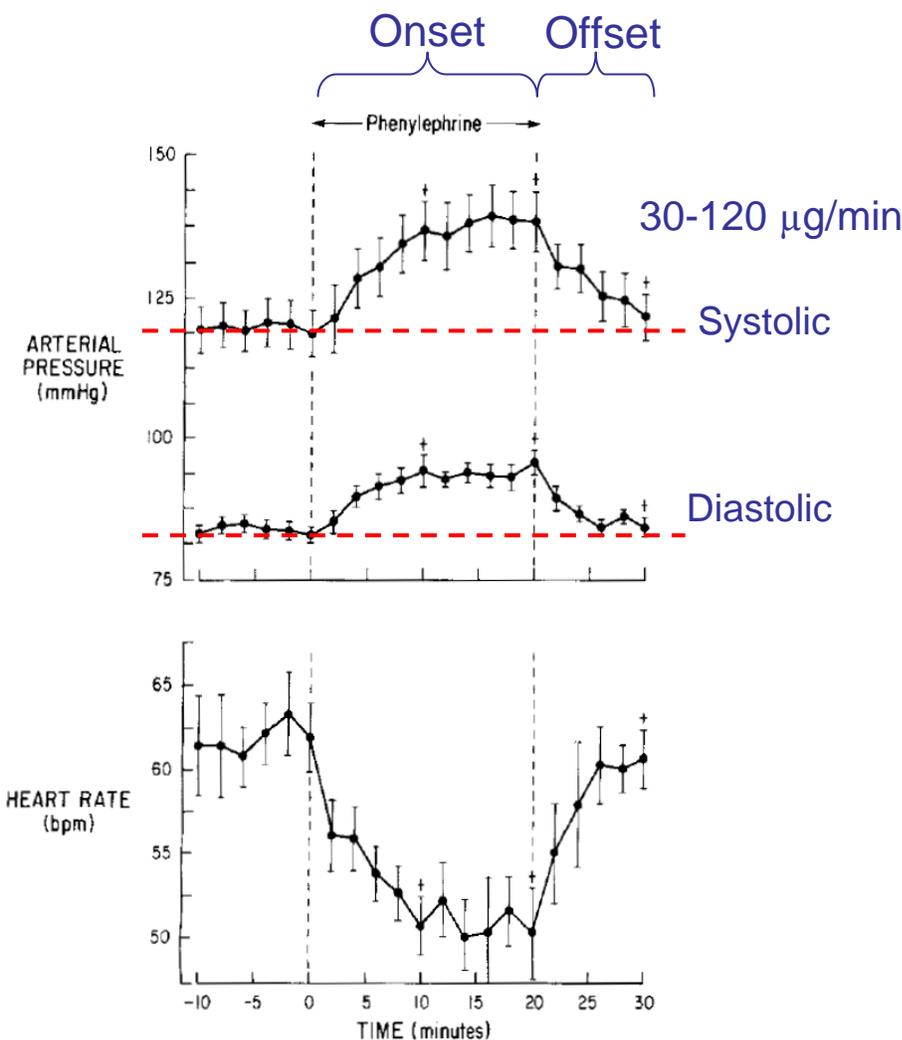


Figure 5: Changes in arterial pressure and heart rate during PE administration as *i.v.* infusion with doses ranging from 30 to 120 $\mu\text{g}/\text{min}$ ($n=8$)¹³.

2.7. What is effect of important intrinsic factors on the response of PE?

Age, Sex, Race

Literature reports evaluating the impact of intrinsic factors (age, sex, race) on blood pressure response of PE is not adequate and/or conclusive. Therefore, dosing recommendations cannot be made to address these factors.

Renal & Hepatic Impairment

There are two reports which evaluate the response to PE in subjects with renal and hepatic impairment^{22, 23}. The studies were conducted using DHVT and PE dose-response curves were constructed and compared between the organ impaired patients *vs* healthy controls (Fig. 6).

Dose-response curve of PE is shifted to the left in ESRD patients (ED_{50} : 38 ng/min to 145 ng/min; 4-fold shift) representing increased sensitivity to PE²². It has to be noted that ESRD patients were also on recombinant human erythropoietin (rHuEPO) therapy which has been shown to demonstrate a direct vasoconstrictive effect *in vitro*, however, the effect is not consistent across all studies. Also, in the current study, rHuEPO did not exhibit vasoconstrictive effect in the control arm. Therefore, lower doses of PE might potentially be required in patients with impaired renal function. On the other hand, liver cirrhosis patients show a marked decrease in sensitivity, with the dose-response curve shifting to the right (ED_{50} : 1514 ng/min to 282 ng/min; 5-fold shift) suggesting a compromised α -adrenergic vasoconstrictive response in liver cirrhosis patients²³. Therefore, higher doses of PE might be required in liver cirrhosis patients.

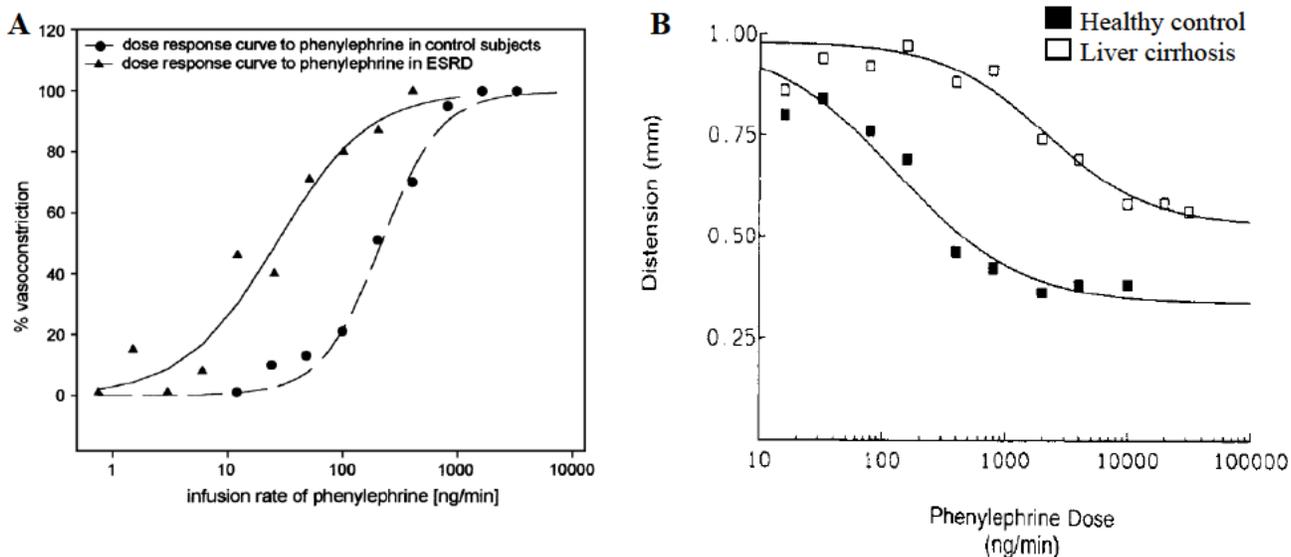


Figure 6: Dose-response curves of PE in ESRD patients (A) and liver cirrhosis patients (B) compared to healthy control subjects^{22, 23}.

2.8. What is the impact of drug interactions on the response of PE?

The reported drug interactions studies were typically evaluated by DHVT, measuring the peripheral vascular resistance and also by systemic blood pressure studies. In case of DHVT studies, dose-response curves for PE were constructed and the ED_{50} was compared in the presence and absence of the interacting drug. In case of systemic blood pressure studies, the PE dose required to raise blood pressure to a pre-defined target (e.g., PD_{20} which is the PE dose required to increase SBP by 20 mmHg) was compared.

Classes of drugs which typically interact with PE response are listed in Table 2. All drug interactions affect the pharmacodynamic response of PE, with the exception of monoamine oxidase inhibitors which interact from a pharmacokinetic perspective i.e., increase systemic exposures to PE. Due to inconsistencies in the results across different articles, it might not be possible to derive a clear, quantitative dose-adjustment addressing these interactions. Providing the direction of the change in sensitivity to PE response is how best these interactions could be addressed. Also, it has to be noted that PE will be administered in a controlled medical setting where hemodynamic variables are continuously or frequently monitored to capture changes in

sensitivity to PE response due to co-medications. In some cases, co-medications are discontinued prior to peri-operative procedures. In cases such as septic shock, PE will be administered as a continuous *i.v.* infusion titrated to a target response.

Table 2: Overview of drugs that interact with the pharmacodynamic response of PE[†].

Interacting drug	Effect
α -adrenergic antagonists (prazosin, trimazosin, terazosin, urapidil)	<ul style="list-style-type: none"> • Dose-response curve shift to right indicating decreased responsiveness to PE • Studies show increase in ED₅₀ by 2- to 4-fold and increase in PD₂₀ by 3- to 7-fold across different α-adrenergic antagonists. Larger than usual PE doses might be required.
α_2 -adrenergic agonist (clonidine)	<ul style="list-style-type: none"> • Increased responsiveness to PE by 2 to 3-fold. Lower doses of PE might be required.
β -adrenergic blocking agents (e.g., propranolol) Calcium channel blockers (nifedipine, diltiazem, verapamil, nifedipine)	<ul style="list-style-type: none"> • May decrease sensitivity to PE as seen in a few studies; however, some studies do not show a significant change in PE response.
Steroids (hydrocortisone)	<ul style="list-style-type: none"> • Enhanced sensitivity to pressor response of PE as they sensitize blood vessels to angiotensin and catecholamines. Lower doses of PE might be required.
Tricyclic antidepressants (desipramine, imipramine)	<ul style="list-style-type: none"> • Increased responsiveness to PE by 2 to 3-fold. Lower doses of PE might be required
Monoamine oxidase inhibitors-like drugs (e.g., procarbazine)	<ul style="list-style-type: none"> • Increased responsiveness to PE by increasing systemic exposures to PE (inhibition of PE metabolism). Lower doses of PE might be required.
ACE inhibitors (enalapril, captopril, ramipril) Angiotensin receptor blockers (losartan, candesartan)	<ul style="list-style-type: none"> • May decrease responsiveness to PE by inhibiting angiotensin II which is a potent endogenous vasoconstrictor. However, majority of the studies do not significantly change the response to PE.

[†] Note: There are several references listed by the sponsor on drug interactions with PE. This review does not list them because no specific dosing recommendations are being provided

2.9. Does PE increase blood pressure in perioperative hypotensive setting?

Twenty nine studies supporting the use of PE for increasing blood pressure during neuraxial anesthesia were submitted by the sponsor. Majority of the literature (25/29) show the use of PE to increase blood pressure to prevent hypotension due to spinal anesthesia during elective cesarean delivery. The review primarily focuses on this clinical setting.

Perioperative hypotension due to neuraxial anesthesia

The evidence that phenylephrine causes an increase in blood pressure comes from a placebo controlled, randomized, double-blind study²⁴. Allen *et al* evaluated four fixed rate PE infusions (25, 50, 75 and 100 µg/min) against placebo in patients undergoing elective cesarean delivery²⁴. PE infusion was started immediately after injection of spinal anesthesia and continued until 10 min after delivery. The mean cumulative dose achieved in the PE groups was 984, 1859, 2144 and 2179 µg in the 25, 50, 75 and 100 µg/min infusion groups, respectively. The cumulative PE dose depended on the time from anesthesia induction to the time of delivery and the number of PE rescue boluses. Hypotension was defined as SBP going below 80% of the baseline. The number of patients experiencing pre-delivery hypotension in the placebo group was significantly higher compared to PE treatment (doses ≥ 50 µg/min). Further a trend for dose-dependent decrease in the number of patients experiencing pre-delivery hypotension was noted (Fig. 7) providing evidence for PE's blood pressure effect in subjects undergoing elective cesarean delivery.

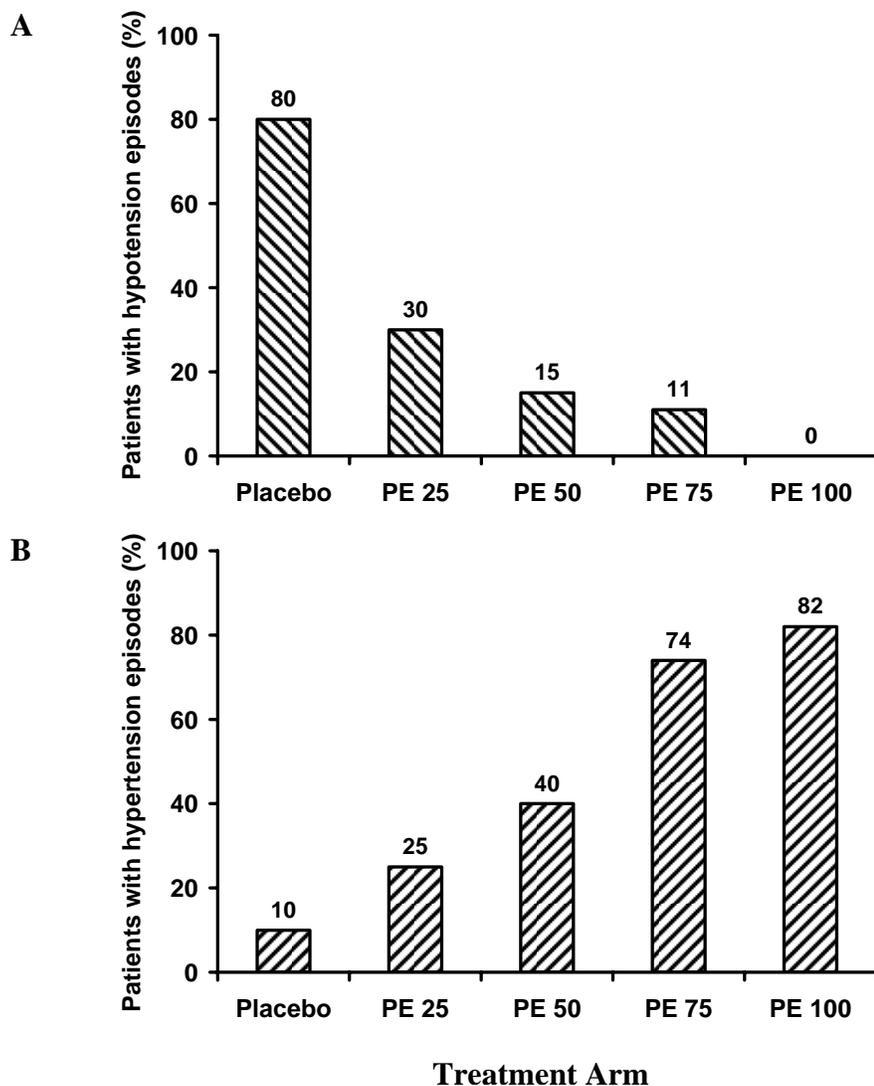


Figure 7: Percentage of patients experiencing hypotensive events (A) and hypertensive events (B) with respect to placebo or PE treatment²⁴.

Summary of PE use in an i.v. bolus setting

Eight publications describing PE use in an *i.v.* bolus setting were reviewed²⁵⁻³². Four out of eight studies used an initial PE bolus dose of 100 μg ²⁵⁻²⁸. Definition of hypotension differed slightly across these studies -- SBP less than an absolute value i.e., 90 or 100 mmHg and/or a percent of baseline, i.e., 70%, 80% or 90%. When hypotension occurred, PE was administered as rescue bolus across all these studies.

- Most of the subjects in these studies received additional PE rescue boluses, since a 100 μg initial bolus alone was not sufficient to keep SBP at or above the pre-defined threshold of hypotension. The mean cumulative PE dose (calculated or reported) used was 160 μg and 175 μg by Prakash *et al*²⁶ and Ramanathan *et al*²⁷, respectively. In the study by Gunda *et al*²⁵, only 3 out of 50

subjects (6%) received an additional PE rescue bolus suggesting better control of blood pressure with a single bolus dose of 100 µg. However, the results should be cautiously interpreted because blood pressure was not frequently monitored and there was a relatively lower threshold for hypotension (≤ 90 mmHg or 70% baseline).

PE was also studied at doses lower than 100 µg in four studies²⁹⁻³².

- Moran *et al*³⁰ studied PE at an initial bolus dose of 80 µg and used rescue PE bolus of 40 µg upon incidences of hypotension. The mean cumulative PE dose achieved in that study was 335 µg, suggesting more frequent hypotensive episodes warranting PE rescue boluses.
- In a study by Tanaka *et al*³¹, almost 50% of the subjects (8/17) failed to respond to PE when receiving doses less than 100 µg (lowest dose=40 µg). Failure or ineffectiveness in this study was defined as the subject developing hypotension (SBP $< 80\%$ baseline) or nausea at any time during the study period in spite of rescue PE bolus given when SBP dropped below baseline. However, majority of the subjects treated with doses above 100 µg, up to a maximum of 120 µg, showed effectiveness according to the study definitions. This study also reported ED₉₅ of PE to be 159 µg (95% CI: 122-371 µg) for the prevention of hypotension and nausea and 135 µg (95% CI: 106-257 µg) for the prevention of hypotension alone.
- Another similar study by George *et al*²⁹ (PE dose range studied: 80-180 µg) reported ED₉₀ of PE for the treatment of hypotension to be 147 µg (95% CI: 98-222 µg).
- Though the calculation of ED₉₅/ED₉₀ is dependent on the study definition of the treatment's success/failure and on the degree of spinal block, these studies give a fair idea on the starting initial PE bolus dose. Of note, the lower 95% CI in both the studies to prevent hypotension was at least 100 µg or above.
- These findings are corroborated by another study by das Neves *et al*³² who investigated the effectiveness of PE as a continuous PE infusion at 0.15 µg/kg/min as against two bolus groups – (i) 50 µg bolus immediately following spinal anesthesia, and (ii) 50 µg bolus following first incidence of hypotension. It is seen that the incidence of hypotension and the percent of patients receiving rescue PE doses were higher in the bolus groups [hypotension: 32.5% (i) and 80% (ii); rescue dose: 30% (i) and 70% (ii)].

Based on the summary of PE bolus studies, the following observations can be made:

1. A 100 µg PE bolus seems to be a reasonable starting dose in the prevention of hypotension due to induction of spinal anesthesia in subjects undergoing elective cesarean delivery. However, it should be noted that additional PE rescue boluses might be required to keep the blood pressure around baseline depending on the extent of spinal block.
2. Doses lower than 100 µg are often associated with higher frequencies of hypotensive episodes requiring more number of PE rescues.

3. Frequent monitoring of hemodynamic variables is essential in the setting of bolus administration to prevent episodes of hypotension occurring over a longer time interval.

Summary of PE use in an i.v. infusion setting

Eight articles describing PE use in an *i.v.* infusion setting were reviewed^{24, 32-38}. The PE dose studied ranged from 0.15 µg/kg/min to 100 µg/min.

- Study by das Neves *et al*³² show that when PE is administered as a continuous *i.v.* infusion at 0.15 µg/kg/min (eqv. 12 µg/min for a 80 kg female), the incidence of hypotension, defined as SBP going less than 80% of baseline, was 17.5%. Only 1/40 (2.5%) subjects developed reactive hypertension, defined as SBP greater than 120% of baseline. Nausea and vomiting incidences were also lower (≤10%) at this PE infusion regimen.
- Langesaeter *et al*³³ studied PE at an infusion rate of 0.25 µg/kg/min (eqv. 20 µg/min for 80 kg female) and reported lower incidences of hypotension (20%) when used with 7 mg bupivacaine. There were no cases of hypertension reported in this study.
- Stewart *et al*³⁴ studied three PE infusion regimens – 25, 50 and 100 µg/min and show lower incidence of hypotension with higher infusion regimens (36%, 16% and 8% for 25, 50 and 100 µg/min, respectively). No episodes of hypertension or bradycardia were reported since PE infusion was stopped when SBP readings went above baseline.
- Allen *et al*²⁴ studied four PE infusion regimens along with a placebo arm – 25, 50, 75 and 100 µg/min and show lower incidence of hypotension with higher infusion regimens (30%, 15%, 11% and 0% for 25, 50, 75 and 100 µg/min, respectively). However, there were higher incidences of bradycardia (32% in 75 and 100 µg/min groups) and hypertension (74% and 82% in 75 and 100 µg/min groups, respectively) with the higher infusion regimen.
- Ngan Kee *et al* studied PE as fixed rate infusion of 100 µg/min across four studies³⁵⁻³⁸. In one study PE was infused at 100 µg/min for a period of 3 min and in the rest for a period 2 min, immediately following spinal anesthesia. From that point until delivery, PE was infused at 100 µg/min, whenever SBP (measured every minute), readings went below baseline. It is observed across all the four studies that the incidence of hypotension was lower (2%, 4%, 23% and 29%). However, this was accompanied by higher incidences of hypertension episodes (21%, 38%, 41% and 47%).

Based on the summary of PE infusion studies, the following observations can be made:

1. In a continuous infusion regimen, PE infusion rates ranging from 12 µg/min to 50 µg/min generally resulted in fewer hypotensive as well as hypertension/bradycardia episodes. It is observed that infusion rates higher than 50 µg/min lead to higher incidences of hypertension.
2. When higher PE dose regimens are chosen (100 µg/min), frequent hemodynamic monitoring is recommended. PE infusion should be stopped when blood pressure rises beyond the baseline

(before the induction of anesthesia) values to prevent significant drop in heart rate and cardiac output.

PE response relative to the dose of the anesthetic agent

Langesaeter *et al*³³ investigated two different spinal anesthesia dosing regimens [7 mg bupivacaine (B7) *vs* 10 mg bupivacaine (B10), in the background of 4 μ g sufentanil] in the absence (Plc) and presence of PE infused at 0.25 μ g/kg/min, on cardiac output and blood pressure³³. It was observed that the distribution of PE rescue bolus, upon incidence of hypotension (defined as SBP going below 90 mmHg), was relatively higher in the B10/PE group (40%) relative to B7/PE group (20%). Moreover, the effect of PE on SBP was similar (as seen by SBP time courses in Fig. 8) between the B7/Plc and B10/PE groups. Similar results were also seen in studies by Ben-David *et al* (10 mg bupivacaine *vs* 5 mg bupivacaine+25 μ g fentanyl) and van de Velde *et al* (9.5 mg bupivacaine *vs* 6.5 mg bupivacaine), where the low dose anesthesia group resulted in fewer incidences of hypotension, nausea and vasopressor rescue medications.

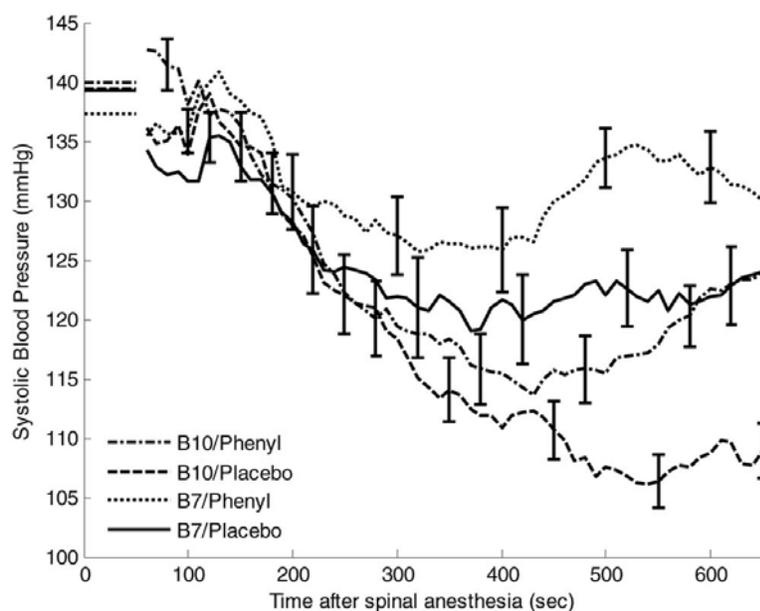


Figure 8: Time course of mean SBP in the four treatment groups³³. Baseline is marked on the y-axis. Error bars represent SE around the mean.

This suggests that the response to vasopressors including PE is dependent on the dosing regimen of the anesthetic agent chosen. The dose of the anesthetic agent should be appropriately chosen, only to provide the minimal adequate spinal block.

Frequency of monitoring hemodynamic variables

Typically all the studies measure hemodynamic variables every minute following anesthesia induction. Less frequent monitoring could miss brief periods of hypotension or hypertension which would require PE rescue boluses or stoppage of infusion, respectively. Frequent and sound monitoring of hemodynamic variables non-invasively seems to be a viable option.

Perioperative hypotension due to general anesthesia

Majority of the studies report the use of PE following induction of general anesthesia in the setting of CABG or other cardiac procedures.

Schwinn *et al*³⁹ studied the dose-response of PE in patients undergoing CABG surgery. Bolus doses of PE ranging from 20 μg to 360 μg was injected intravenously before and during anesthesia (isoflurane/oxygen) and the peak MAP in the ensuing 2 min was recorded. Dose titration was continued until the peak MAP response to PE increased 20% above baseline. Incremental bolus doses were administered 5 min after the peak MAP had returned to baseline from the previous dose. Bolus doses of PE were preferred since administration of continuous infusion could increase the afterload in patients with myocardial disease and potentially increase myocardial wall stress and oxygen consumption. PE produced a dose-dependent increase in MAP in both (i) pre-anesthesia as well as in the group (ii) following anesthesia induction (Fig. 9). The calculated mean PD_{15} values i.e., the PE dose required to cause a 15 mmHg increase in MAP were 115 μg and 124 μg in groups (i) and (ii), respectively. The results show that PE causes a dose-dependent increase in MAP in patients undergoing CABG surgery with a rapid onset of action.

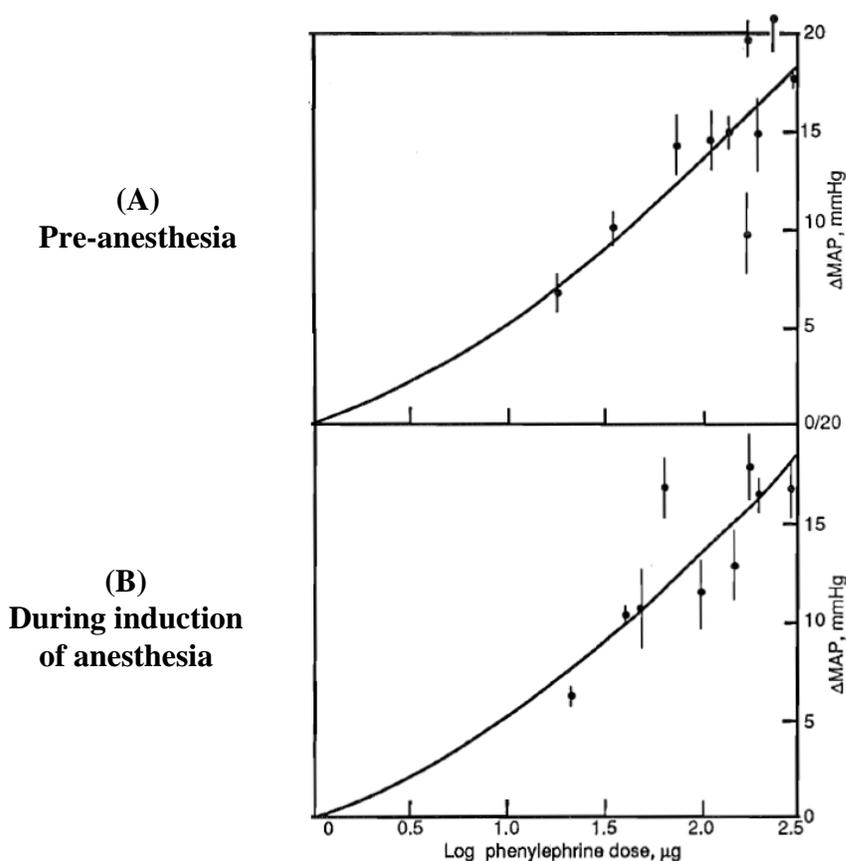


Figure 9: Dose-response curve for PE before (A) and during anesthesia (B)³⁹

In addition, from other studies submitted in this setting, PE showed a rapid increase in mean arterial pressure when used as an *i.v.* bolus from 50 to 250 μg or as an *i.v.* infusion from 0.50 to 1.4 $\mu\text{g}/\text{kg}/\text{min}$ ⁴⁰⁻⁴³.

2.10. Does PE increase MAP in patients with septic shock?

Six studies describing the use of PE to increase MAP in septic shock patients (or) patients with sepsis who are otherwise normotensive are reviewed⁴⁴⁻⁴⁹:

- Bellissant *et al*⁴⁴: Dose-response study in septic shock patients
- Morelli *et al* and Jain *et al*^{46, 47}: Randomized studies comparing the efficacy of PE vs norepinephrine in septic shock patients
- Gregory *et al*⁴⁸: Non-randomized studies evaluating the efficacy of PE as first-line treatment in septic shock patients
- Flancbaum *et al* and Yamazaki *et al*^{45, 49}: Non-randomized studies evaluating the efficacy of PE in septic patients who are otherwise normotensive

Bellissant *et al* studied the dose-response of PE in septic shock patients as against healthy controls in the presence and absence of treatment with hydrocortisone (sensitizes blood vessels to angiotensin and catecholamines). In this study, PE was infused in a stepwise manner at 0.01, 0.02, 0.05, 0.07, 0.1, 0.2, 0.5, 0.75, 1, 1.5, 3, 4.5, 6, 9 and 12 $\mu\text{g}/\text{kg}/\text{min}$. Each dose was maintained for 5 min and MAP was determined as the mean value recorded within the last minute of infusion. Mean change from baseline in MAP was the response variable.

Dose-response for PE was observed in septic shock patients and healthy controls; however, with a reduced sensitivity to PE in septic shock patients (Fig. 10). The maximum observed MAP response from baseline was ~ 30 mmHg at 6 $\mu\text{g}/\text{kg}/\text{min}$ PE infusion, with no additional incremental effect upon increasing the PE dose. It should be noted that the study did not allow for the MAP response to reach baseline before each PE titration. However, that should not be of a concern, since PE will be administered in a similar manner as titrated to a target response in a shock setting.

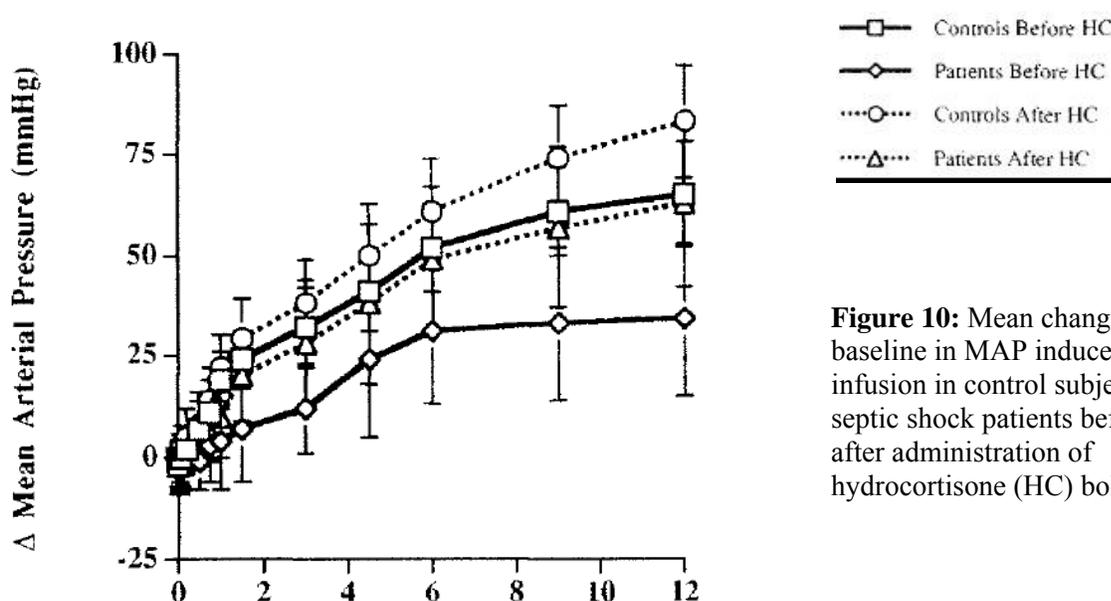


Figure 10: Mean change from baseline in MAP induced by PE infusion in control subjects and septic shock patients before and after administration of hydrocortisone (HC) bolus⁴³.

In a non-randomized study, Flancbaum *et al*⁴⁵ evaluated the dose-response of PE in critically ill, septic surgical patients who were otherwise normotensive. PE was infused for 3 h at progressively increasing rates of infusion of 0.5, 1, 2, 3, 4 and 8 $\mu\text{g}/\text{kg}/\text{min}$ at 30 min intervals with measurements taken at the end of each infusion. A dose dependent increase in MAP was observed in this study (Fig. 11), similar to that seen in the study by Bellissant *et al*, with no additional increase in MAP at higher infusion rates. Given the rapid onset of action associated with PE, it is not clear as to why a 30 min duration for increasing the rate of infusion was chosen.

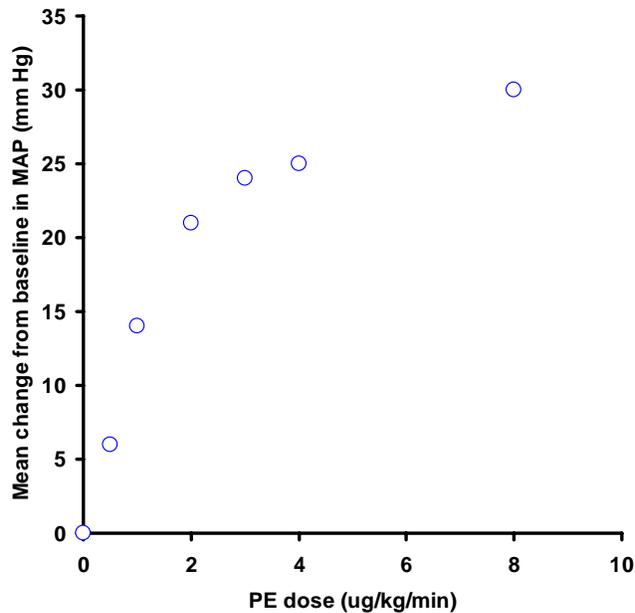


Figure 11: Mean change from baseline in MAP induced by PE infusion in septic patients who are otherwise normotensive⁴⁵.

In the two randomized studies by Morelli *et al*⁴⁶ and Jain *et al*⁴⁷, PE was compared against an active comparator, norepinephrine, in patients with septic shock. In both the studies, PE was administered as *i.v.* infusion, titrated to achieve and maintain a pre-defined target in MAP. Both studies showed that PE increased and maintained MAP successfully at the desired target during the entire duration of treatment. Mean of the maximum PE infusion rate at any time during the treatment is shown in Table 3. In another non-randomized study by Gregory *et al*, 13 patients with septic shock (persistent hypotension with MAP <65 mmHg) were treated with PE infusion ranging from 0.5 to 9.0 $\mu\text{g}/\text{kg}/\text{min}$ to increase and maintain MAP >70 mmHg. Results showed that initial MAP stabilization was rapid (>70 mmHg) which required a mean PE infusion rate of 1.3 $\mu\text{g}/\text{kg}/\text{min}$ (Table 3).

Table 3: Study features and results – Morelli *et al*, Jain *et al* and Gregory *et al*⁴⁶⁻⁴⁸.

Article	PE dose range, $\mu\text{g}/\text{kg}/\text{min}$	Target MAP, mmHg	Mean PE dose, $\mu\text{g}/\text{kg}/\text{min}$	Mean MAP, mmHg		
				Baseline	End of PE infusion	Change from baseline
Morelli <i>et al</i>	NR	65 to 75	2.85 ^a	54	68.5	14.5
Jain <i>et al</i>	0.5 to 8.5	> 75	3.28 ^a	49	79	30
Gregory <i>et al</i>	0.5 to 9.0	> 70	3.70 ^a 1.30 ^b	57	75	18

NR Not Reported

^a average of maximum PE dose at anytime during treatment

^b average of PE dose for initial stabilization MAP >70 mmHg

The studies put together show that PE causes an increase in MAP in septic patients who are hypotensive or normotensive. The required PE dose will depend upon the target at which MAP is intended to be stabilized. Based on the two dose-response studies, it can be concluded that, infusion rates beyond 4 to 6 $\mu\text{g}/\text{kg}/\text{min}$ might not result in additional incremental response in MAP. Since, the requirement in a septic shock setting is to increase and maintain MAP at a set target during the entire duration of treatment i.e., stabilization leading to recovery from shock, PE is best given as infusion titrated frequently, to achieve the target MAP.

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/s/

SUDHARSHAN HARIHARAN
08/15/2012

RAJANIKANTH MADABUSHI
08/15/2012

**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	203826	Brand Name	--
OCP Division (I, II, III, IV, V)	I	Generic Name	Phenylephrine HCl
Medical Division	DCRP	Drug Class	α_1 adrenergic agonist
OCP Reviewer(s)	Sudharshan Hariharan	Indication(s)	To increase blood pressure in acute hypotensive and perioperative states
OCP Team Leader	Raj Madabushi	Dosage Form	Sterile solution for injection
Pharmacometrics Reviewer	--	Dosing Regimen	Intravenous infusion titrated to effect. Regimens vary based on hypotensive states. Refer product insert.
Date of Submission	01/12/2012	Route of Administration	Intravenous
Estimated Due Date of OCP Review	09/12/2012	Sponsor	West-Ward Pharmaceutical Corp.
Medical Division Due Date	10/12/2012	Priority Classification	Standard; 505(b)(2)
PDUFA Due Date	11/12/2012		

Summary

Phenylephrine is a selective α_1 adrenergic agonist causing vasoconstrictive (pressor) effects. The proposed indication is for increasing blood pressure in acute hypotensive states such as shock and in other perioperative hypotensive settings. The proposed drug product is a sterile solution for intravenous injection containing phenylephrine HCl as the active ingredient (USP 10 mg/mL).

Phenylephrine HCl injection, USP has historically been marketed under the "Grandfather" exemption in Section 201(p)(1) of the Federal Food Drug and Cosmetic Act. The sponsor intends to rely solely on published literature to support the non-clinical, clinical pharmacology, clinical safety and efficacy of the proposed phenylephrine HCl injection.

The clinical pharmacology package consists of published literature which primarily addresses the following:

- Pharmacokinetics following *i.v.* administration in healthy subjects
- Mass balance and metabolism
- Pharmacodynamics -- vasoconstrictive effects by age, race, sex, pregnancy, hepatic impairment, renal impairment and disease condition such as diabetes, congestive heart failure and hypertension
- Drug interactions -- pharmacodynamic effects -- with α adrenergic agonists, α adrenergic antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, calcium channel blockers, cardiovascular drugs, CNS drugs, inhalation anesthetics, anticholinergics, tricyclic antidepressants, steroids and antidiabetic drugs
- Cardiac safety (QT prolongation)
- Dose- and exposure-response in healthy subjects and patients --effect on blood pressure, mean arterial pressure and heart rate

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

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

	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	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
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	Relies on published literature
5	Has a rationale for dose selection been submitted?			X	
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			
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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			An attempt has been made
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	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
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			

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

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](#)

Sudharshan Hariharan	03/14/2012
Reviewing Clinical Pharmacologist	Date
Raj Madabushi	03/14/2012
Team Leader/Supervisor	Date

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/s/

SUDHARSHAN HARIHARAN
03/17/2012

RAJANIKANTH MADABUSHI
03/18/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-826	Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	December 28, 2011		
Division:	Division of Cardiovascular and Renal Products	Team Lead: Angelica Dorantes, PhD	
Sponsor:	West-Ward Pharmaceutical Corp.	Acting Supervisor: Angelica Dorantes, PhD	
Trade Name:	Phenylephrine HCl Injection, USP	Date Assigned:	January 24, 2012
Established Name:	Phenylephrine HCl	Date of Review:	March 7, 2012
Indication:	Treatment of acute hypotension	Type of Submission: Original New Drug Application – 505(b)(2)	
Formulation/ strengths	Solution for injection/ 10 mg/mL		
Route of Administration	IV injection		
<u>SUBMISSION:</u>			
<p>The proposed drug product is a sterile solution for IV injection containing phenylephrine HCl as the active ingredient and is indicated for the treatment of acute hypotensive states such as shock and perioperative hypotension. Phenylephrine hydrochloride is a selective α1-adrenergic receptor agonist and vasoconstrictor. It is commonly used for temporary relief of nasal congestion and there are several phenylephrine containing combination drugs including ophthalmic solutions. Phenylephrine hydrochloride Injection is an unapproved “grandfathered” drug product marketed by Baxter HealthCare. A commercial IND 109,977 was filed by Baxter and the firm met with the clinical division in November, 2010 to discuss the possible approval of an NDA under 505(b)(2) based on literature data. On May 2, 2011, West-Ward Pharmaceuticals purchased Pre-IND 109,977 and the associated rights thereof.</p>			
<u>BIOPHARMACEUTIC INFORMATION:</u>			
<p>There is no reference listed drug for phenylephrine hydrochloride HCl Injection available in the electronic orange book at this time. The Applicant proposes to rely on published literature to support the safety, effectiveness and human PK of the proposed drug product. In order to link the proposed drug product with the published literature, the Applicant was asked, in an information request letter dated 2/15/2012, to:</p> <p><i>Provide a side-to-side comparison table showing that the qualitative and quantitative composition (including all active and inactive ingredients) of your proposed to-be-marketed Phenylephrine HCl drug product is the same as the formulation of the Phenylephrine HCl drug product used in each one of the published PK studies supporting your NDA. If the formulations are not the same, provide a justification for any difference in the composition of the formulations.</i></p>			

The Applicant responded in an NDA amendment dated 3/1/2012, as follows:

The composition of the formulation of the Phenylephrine HCl Injection, USP drug product used in the PK studies is qualitatively and quantitatively the same (including all active and inactive ingredients) as our proposed to-be-marketed Phenylephrine HCl drug product. Phenylephrine HCl Injection, USP 10 mg/mL, Lot No. P050327 was used in the PK studies, which is also one of the three submission batches manufactured to support our original NDA 203-826 submission. Please refer to the side-by-side comparison in the table below:

**Phenylephrine HCl Injection, USP side-by-side comparison between
proposed to be marketed Phenylephrine HCl Injection, USP drug product versus Phenylephrine HCl drug product
used in the PK studies**

Phenylephrine HCl Injection, USP Lot No. P050327 - Proposed to be marketed	Function	Component Quantity	Phenylephrine HCl Injection, USP Lot No. P050327- Used in the PK studies	Function	Component Quantity
		Per 1 mL			Per 1 mL
Phenylephrine HCl, USP	Active Ingredient	10 mg	Phenylephrine HCl	Active Ingredient	10 mg
Sodium Chloride, USP	(b) (4)	(b) (4)	Sodium Chloride, USP	(b) (4)	(b) (4)
Sodium Citrate Dihydrate, USP	(b) (4)	(b) (4)	Sodium Citrate Dihydrate, USP	(b) (4)	(b) (4)
Citric Acid Monohydrate, USP	(b) (4)	(b) (4)	Citric Acid Monohydrate, USP	(b) (4)	(b) (4)
Sodium Metabisulfite, USP	(b) (4)	(b) (4)	Sodium Metabisulfite, USP	(b) (4)	(b) (4)
Sodium Hydroxide NF	(b) (4)	As needed to adjust pH	Sodium Hydroxide NF	(b) (4)	As needed to adjust pH
Hydrochloric Acid, NF	(b) (4)	As needed to adjust pH	Hydrochloric Acid, NF	(b) (4)	As needed to adjust pH
Water For Injection, USP	(b) (4)	Quantity Sufficient	Water For Injection, USP	(b) (4)	Quantity Sufficient

The above table indicates that the to-be-marketed formulation and the formulation used in the PK studies are the same. However, the Applicant did not point out that these are the animal PK studies where Lot No. P050327 of their phenylephrine Injection product was used. The response was discussed with the Clinical Pharmacology reviewer, Sudharshan Hariharan, Ph.D. The evaluation and acceptability of the human PK data from the literature (using unknown formulations of the drug product) will be determined by the Clinical Pharmacology Reviewer from OCP. Therefore, further involvement of the ONDQA-Biopharmaceutics review team for the evaluation of this NDA is not longer needed.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 203-826 is fileable. However, this NDA does not require further assessment by the ONDQA-Biopharmaceutics team.

Signature

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Biopharmaceutics Team Leader/ Supervisor
Office of New Drug Quality Assessment

cc: NDA 203-826/DARRTS

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ELSBETH G CHIKHALE
03/08/2012

ANGELICA DORANTES
03/08/2012