

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203826Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 203-826 Phenylephrine HCl Injection
Product Name:

PMR/PMC Description: Conduct a study in the ≥ 12 - 16 year old age group to evaluate the dose effect of phenylephrine hydrochloride injection on blood pressure in patients undergoing general anesthesia and neuroaxial anesthesia. Administration by both the bolus and infusion methods must be studied for the treatment of hypotension. Dosing of phenylephrine should be weight-based since weight may be quite variable in this population. The information you capture needs to include, at a minimum, the following:

- Demographic and medical history information that informs about the subjects' cardiovascular status.
- Concomitant intraoperative and post-operative medications, including their doses and adjustments in inhaled gas concentration or intravenous agent infusion rates.
- Interventions used to treat the hypotension, e.g., other pressor agents, intravenous fluid boluses, changes in patient positioning.
- Intraoperative events relevant to subjects' physiological status, such as blood loss and fluids administered.
- Blood pressures and heart rate, time to onset and maximal response and duration of response should be defined and captured before and during the treatment.
- Pharmacokinetics of the proposed product need to be characterized at points relative to the phenylephrine administration.

Propose a means of reporting safety data in the ≥ 12 - 16 year old age group that best informs the prescriber about the risk:benefit of different dose levels of phenylephrine.

Below are our suggested numbers and timelines:

50 subjects in bolus treatment group / 50 subjects in infusion treatment group

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/20/2013</u>
	Study/Trial Completion:	<u>12/20/2016</u>
	Final Report Submission:	<u>05/23/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
 Life-threatening condition

- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies are completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to provide information for labeling for the relevant pediatric population (12-16 years old). Specifically, the study will provide information on the dosing needed to confer the pharmacodynamic effect and safety.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

RD:

C Breder 12-20-12
MR Southworth 12-20-12

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

/s/

QUYNH M NGUYEN
12/20/2012

505(b)(2) ASSESSMENT

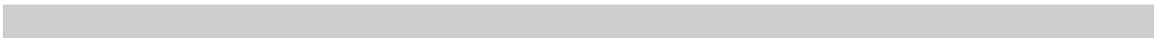
Application Information		
NDA # 203-826	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: Phenylephrine HCl Injection Dosage Form: Injection Strengths: 10 mg/mL		
Applicant: West-Ward Pharmaceutical Corp.		
Date of Receipt: 11-29-12 (resubmission)		
PDUFA Goal Date: 1-29-13	Action Goal Date (if different): 12-20-12	
Proposed Indication(s): For increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Non-clinical data, clinical pharmacology (human PK) data, clinical safety and efficacy data

*each source of information should be listed on separate rows

The non-clinical literature that is necessary for approval is relevant because in the vast majority of studies utilizing animals from rodents to non-human primates, phenylephrine injected intravenously evoked an increase in arterial blood pressure via activation of alpha-1 adrenoreceptors.

The clinical pharmacology literature submitted by the sponsor is relevant because it provides support for the following sections -- (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.

The clinical literature submitted by the sponsor provides relevant support for efficacy and safety based on consistent findings by independent groups across multiple studies.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

1. There is no reference listed drug for phenylephrine HCl, USP available in the electronic orange book at this time.

2. Phenylephrine HCl, USP is an aqueous solution¹. The drug substance, phenylephrine, is freely soluble in water with a solubility of 10g/100mL². Therefore, solubilizing agents are not part of the formulation composition.

3. Phenylephrine is administered intravenously. Therefore, no bioavailability issues exist between the formulations studied in published literature and phenylephrine HCl, USP.

These points provide rationale for bridging the formulations implicitly.

¹ Section 3.2 in NDA submission: Drug Product: Description and Composition

² Section 3.2.S.1.3 in NDA submission: General Properties: Physicochemical Properties

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

QUYNH M NGUYEN
12/20/2012

There are multiple manufacturers of this product currently in the marketplace with the proposed concentration and package configuration. Delaying the approval of this application would prevent the most appropriate clinical information and other product information to promote the safe use of the product from being available to practitioners.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This product will be approved for use in an emergent situation in a hospital setting. However, the proposed concentration and package configuration is not ready to use for this setting. The proposed concentration is presently 100 times more concentrated than a practitioner needs and is required to administer in an emergent situation to control a patient’s blood pressure.

Thus, the primary goal of the PMC is for the applicant to develop an appropriate formulation, in an appropriate concentration, in a ready-to-use packaging configuration, that supports the dosage and administration for the indications of use.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A risk assessment or another appropriate methodology will be utilized to guide the applicant in the design of an appropriate ready-to-use product for intravenous bolus administration. The risk assessment is not intended to be performed in lieu of developing a ready-to-use formulation. A risk assessment should utilize a recognized risk assessment tool (e.g., Failure Mode and Effects Analysis). The Applicant should use a multidisciplinary team that includes one or more experts familiar with conducting risk assessments in addition to healthcare professionals that currently practice and prepare and/or administer phenylephrine. The goal of the risk assessment or other appropriate methodology is to determine acceptable approach(s) to the development of a new concentration and package configuration of phenylephrine hydrochloride for intravenous bolus administration that can help mitigate medication errors and unsafe injection practices.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

X Other

The Applicant will utilize an appropriate methodology, such as a comprehensive risk assessment with a multidisciplinary team, to guide the design of an appropriate ready-to-use product for intravenous bolus administration. The Applicant will use the findings of their study to develop an appropriate formulation of phenylephrine hydrochloride, in an appropriate concentration, that supports the dosage and administration for the indications of use.

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

QUYNH M NGUYEN
11/09/2012

IRENE Z CHAN
11/09/2012

SCOTT M DALLAS
11/13/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	PHENYLEPHRINE HYDROCHLORIDE injection, for intravenous use
Applicant	West-Ward Pharmaceutical Corp.
Application/Supplement Number	NDA 203826/S-1
Type of Application	Original NDA
Indication	Increasing blood pressure in adults with clinically significant important hypotension
Established Pharmacologic Class ¹	Alpha-1 adrenergic receptor agonist
Office/Division	ODEI/DCRP
Division Project Manager	Quyhn Nguyen
Date FDA Received Application	December 28, 2011
Goal Date	November 9, 2012
Date PI Received by SEALD	November 5, 2012
SEALD Review Date	November 6, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Some of the headers in HL are shifted to the right (e.g., Dosage Forms and Strengths, Adverse Reactions, Drug Interactions).*

- YES** 4. White space must be present before each major heading in HL.

Comment: *This is not a format deficiency; however, there are two spaces before the Dosage and Administration header in HL (instead of one space).*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Add an identifier after "Dilute before administration" under the Dosage and Administration header (2.1) Also I think the identifier for "Intravenous bolus administration 50 mcg to 250 mcg is 2.4; not (b)(4) I think the identifier for "Antagonist effects on and by alpha-adrenergic blocking agents is 7.2; not (b)(4). Consider adding two bullets in the Drug Interactions header to separate the two distinct Drug Interactions.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- Comment:**
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.
- Comment:**
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
- Comment:**
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
- Comment:**

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- Comment:**
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
- Comment:**
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
- Comment:**
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
- Comment:**

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
- Comment:**

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
- Comment:**

Selected Requirements of Prescribing Information

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[*see Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

N/A

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

YES

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ERIC R BRODSKY
11/06/2012

LAURIE B BURKE
11/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: October 25, 2012

Reviewer: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Phenylephrine Hydrochloride Injection, USP, 10 mg/mL

Application Type/Number: NDA 203826

Applicant/sponsor: West Ward Pharmaceuticals

OSE RCM #: 2012-590

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised vial label and carton labeling for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL, submitted on October 23, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the vial label and carton labeling under OSE Review 2012-590, dated October 12, 2012.

2 MATERIALS REVIEWED

DMEPA reviewed the following label and labeling:

- Vial label submitted on October 23, 2012 (see Appendix A)
- Carton labeling submitted on October 23, 2012 (see Appendix A)

Additionally, our recommendations in OSE Review 2012-590, dated October 12, 2012 were reviewed to assess whether the aforementioned labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the Applicant implemented our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

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

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

/s/

IRENE Z CHAN
10/25/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: October 12, 2012

Reviewer: Ray Ford, RPh
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Phenylephrine Hydrochloride Injection, USP, 10 mg/mL

Application Type/Number: NDA 203826

Applicant/sponsor: West Ward Pharmaceuticals

OSE RCM #: 2012-590

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Phenylephrine Hydrochloride Injection, NDA 203826, for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

This application is a 505(b)(2) submission for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL, packaged as a 1 mL single dose vial. There is no Reference Listed Drug for Phenylephrine Hydrochloride Injection, USP. If approved, this will be the first FDA approved phenylephrine hydrochloride injection, although it has been available and marketed as an unapproved product for many years. The Applicant intends to rely on published medical literature to support the nonclinical profile, clinical pharmacology, clinical safety and efficacy of this product.

The sponsor will not pursue a proprietary name for this drug per a June 18, 2012 email from West Ward Pharmaceuticals. Instead, the sponsor will market this drug under the established name, Phenylephrine Hydrochloride Injection, USP.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 28, 2011 submission:

- Active Ingredient: Phenylephrine Hydrochloride
- Indication of Use: Increasing blood pressure in acute hypotensive states, such as shock, and in perioperative hypotensive settings
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 10 mg/mL
- Dose and Frequency:

- ***Dosing for (b) (4) Perioperative Hypotension***

- 50 micrograms to 250 micrograms by intravenous bolus administration
- 0.5 micrograms/kg/min to 1.4 micrograms/kg/min, titrated to effect by intravenous continuous infusion

- (b) (4)

- ***Dosing for Acute Hypotension in Patients with Septic Shock***

- (b) (4) micrograms/kg/min to (b) (4) micrograms/kg/min, titrated to effect, by intravenous continuous infusion

- ***Dosing for Acute Hypotension in Children***

- (b) (4)

- How Supplied: 1 mL single dose vial, packaged in a carton containing 25 vials
- Storage: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure System: Vial (b) (4) Type I glass, (b) (4)

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the FDA Adverse Event Reporting System (AERS) database and Institute for Safe Medication Practices (ISMP) newsletters for Phenylephrine Hydrochloride Injection medication error reports. We also requested additional data from the Institute for Safe Medication Practices (ISMP)****. Additionally, we reviewed the proposed Phenylephrine Hydrochloride Injection vial labels, carton, and insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) for medication errors cases using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	June 16, 2012
Drug Names	Phenylephrine Hydrochloride (Active Ingredient) Phenylephrine Hydrochlorid% (Verbatim Term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT Route of Administration: Intravenous, Subcutaneous, Intrathecal, Intravenous Bolus, Intravenous Drip No time limits

The AERS search identified 14 reports. Each report was reviewed for relevancy and duplication. After individual review, 10 reports were not included in the final analysis for the following reasons:

Adverse events not related to a medication error

Foreign cases involving phenylephrine confusion with pyridostigmine or dexamethasone due to foreign labels and labeling with no further details

Patient did not have Phenylephrine on medication profile

Device malfunction that has been reported to MAUDE (see ISR #6971442)

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Phenylephrine administered that was not ordered with no additional details

Phenylephrine was concomitant medication only

2.2 MEDICATION ERROR REPORTING PROGRAM (MERP) ****

ISMP searched the Medication Error Reporting Program (MERP) for additional cases and actions concerning phenylephrine hydrochloride injection using the strategy listed in Table 2.



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2.4 ISMP NEWSLETTERS

We searched the ISMP^{***} newsletters for additional cases and actions concerning phenylephrine hydrochloride injection using the strategy listed in Table 2.

(b) (4)

2.5 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,² along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Labels submitted December 28, 2011 (Appendix B)
- Carton Labeling submitted December 28, 2011 (Appendix C)
- Insert Labeling submitted April 27, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and ISMP searches and label and labeling risk assessment.

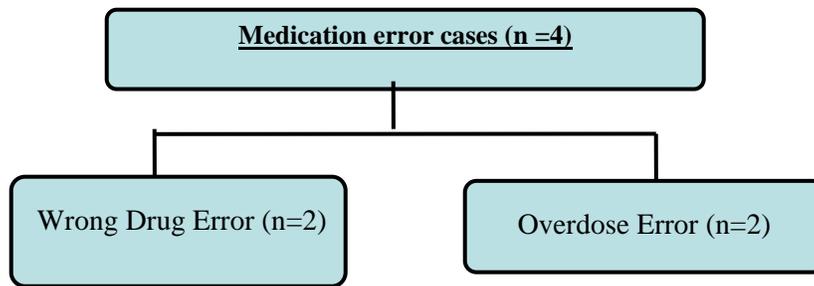
² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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3.1 AERS MEDICATION ERROR CASES

Following exclusions as described in section 2.1, four cases involving Phenylephrine Hydrochloride Injection remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of medication error cases identified in AERS that are included in the review by type of error. Appendix D provides listings of all ISR numbers for the medication error cases summarized in this review. Table 3 in Appendix E contains a more detailed listing of the cases.

Figure 1: Phenylephrine Hydrochloride Injection medication errors in AERS (n = 4) categorized by type of error



▪ **Overdose of phenylephrine cases (n=2):**

We identified two cases of phenylephrine overdose. In the first case (ISR# 678468), a patient was administered 60 mg of Phenylephrine 1% intravenously followed by another 70 mg 45 minutes later. The outcomes were hypertension, pulmonary edema, and ventricular bigeminy. In the second case (ISR# 5633133), a patient received phenylephrine 10 mg rather than 50 micrograms as ordered.

The overdose cases prompted us to review the proposed insert labeling. Our review of the proposed insert labeling identified areas of vulnerability that can be improved to minimize confusion that could lead to dosing errors (see Section 5 for our recommendations).

▪ **Wrong Drug cases (n=2)**

We identified two wrong drug errors. In the first case (ISR# 5874298 year 2008) a patient received phenylephrine (10 mg/mL) instead of metoclopramide (10 mg/2 mL). The reporter indicated the phenylephrine label was white with fuchsia or hot pink lettering for drug name and white lettering on a navy blue background for the strength whereas the metoclopramide label was white with white lettering on a grape colored background for drug name and white lettering on a navy blue background for

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

strength. However, the case does not indicate the manufacturer for either drug. Therefore, we could not verify the accuracy of the report and screen for label similarity that may have led to selection error.

In the second case (ISR#3443839 year 2000), a patient received phenylephrine instead of nubain. Outcomes reported included tingling fingers, headache, and increased blood pressure. The case did not indicate whether the error was due to labels or labeling. According to Drugs@FDA and Orangebook, Nubain (nalbuphine) has a discontinued marketing status. We only found carton labeling for comparison. The nubain vial label was not available from the commonly used DMEPA databases; therefore, no additional action based on this case is necessary at this time.

3.2 MEDICATION ERROR REPORTING PROGRAM (MERP) ****

(b) (4)

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² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

3.5 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT****

Our review of the medication errors retrieved from the AERS database, Quantros MedMarx database, MERP database, and ISMP newsletters identified compounding errors, overdose errors, and wrong drug errors. Additionally, our review of the proposed insert labeling identified areas of vulnerability that can be improved to minimize confusion that could lead to dosing errors. The proposed phenylephrine hydrochloride injection package insert has confusing tables, tables without titles, lacks instructions for using the tables, and contains abbreviations found on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations.

The Applicant has proposed a single strength of 10 mg/mL supplied in a 1 mL vial, which will be required to cover both bolus intravenous administration and continuous infusion. Although the strength is presented in mg/mL, the dosage and administration proposed for this product is based on micrograms instead of milligrams, which creates an inconsistency in units utilized within the labels and labeling. DMEPA generally recommends that product strengths and dosage and administration be consistent in units of measure; however, phenylephrine hydrochloride has been available on the market unapproved for many years as a 10 mg/mL strength. Changing the strength presentation at this time, given the marketing history of phenylephrine hydrochloride, may lead to confusion and unforeseen consequences including new types of medication errors. Therefore, at this time, DMEPA does not propose changing the strength presentation from mg/mL to mcg/mL for the 1 mL vial.

**** This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) which cannot be shared outside of the FDA. Users wanting this information must contact a designated individual in the Division of Medication Error Prevention who will gain approval from ISMP.

The proposed package insert provides dosing for intravenous bolus ranging from (b) (4) mcg to 250 mcg; however, the volume of 10 mg/mL injection needed to achieve doses ranging from (b) (4) mcg to 250 mcg would be (b) (4) mL to 0.025 mL. These volumes cannot be accurately measured with the usual instruments available in hospital settings, and will require healthcare professionals to first prepare a dilute concentration. This introduces opportunity for calculation and compounding confusion that can lead to dosing errors.

Additionally, based on discussion within the Agency, we have received anecdotal information that suggests that diluted solutions of phenylephrine are sometimes prepared in the surgical units rather than by the pharmacy. This raises additional concerns such as a heightened risk of calculation and compounding confusion in a high stress environment like a surgical unit, especially if the solution is prepared in response to a patient who develops acute hypotension while undergoing surgical procedures under anesthesia. Additionally, healthcare professionals in a surgical unit would be preparing a phenylephrine hydrochloride diluted solution in the same area where multiple other products and medication syringes may be present, which also increases the risk for confusion that can lead to medication error. In some cases, these diluted solutions are prepared and stored in stock bottles (without necessarily having a preparation date or expiration date noted) for use with different patients for bolus administration, which raises sterility and stability concerns and promotes unsafe sterile technique and injection practices. For these reasons, we recommend the Division request that the Applicant develop an appropriate concentration and packaging configuration (i.e. 100 mcg/mL multiple-dose vial) that will be commercially available for healthcare professionals to minimize the risks of calculation and compounding errors as well as unsafe sterile technique and injection practices.

The proposed dosing for continuous intravenous infusion ranges from (b) (4) mcg/kg/min to (b) (4) mcg/kg/min, which requires the compounding of a diluted intravenous phenylephrine solution. We note that the currently proposed dosage and administration section of the insert labeling does not provide any directions regarding what intravenous solutions are compatible with phenylephrine hydrochloride. There are also no directions on how to prepare a dilute intravenous phenylephrine solution for continuous infusion and what the final concentration should be. This information should be included in the insert labeling by the Applicant.

With regards to compounding errors, we reviewed the proposed package insert and determined that there are dosing tables under section 2.2 Dosage Calculations that are confusing and not clearly titled. We recommend replacing them with clearer directions for how to dilute phenylephrine when compounding solution for bolus administration if the applicant is not required to market a lower concentration dosage formulation prior to approval of this application.

(b) (4)

4 CONCLUSIONS

DMEPA concludes that the Applicant has not provided appropriate concentrations to support the proposed dosage and administration of this product. Additionally, the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, mitigate confusion, and clarify information. We recommend that our recommendations in Section 5 below be implemented prior to the approval of this NDA.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

A. General Comment

(b) (4) The proposed package insert provides dosing for intravenous bolus ranging from (b) (4) mcg to 250 mcg. However, the Applicant only proposes a single strength of 10 mg/mL. In order to achieve doses as small as (b) (4) mcg to 250 mcg, one or more dilutions would need to be performed by a pharmacist or technician, which introduces opportunity for calculation and compounding confusion that can lead to dosing errors. Therefore, the Applicant has not provided appropriate concentrations to support the proposed dosage and administration of this product. For these reasons, we recommend the Division request that the Applicant develop an appropriate ready-to-use concentration and packaging configuration (i.e. 100 mcg/mL multiple dose vial) to administer the approved intravenous bolus doses. A ready-to-use concentration and packaging configuration will help mitigate the risks of calculation and

compounding errors as well as unsafe sterile technique and injection practices. If this is not possible prior to the approval of this application, then DMEPA recommends that this be included as a postmarket commitment (PMC).

B. Insert Labeling:

1. In the Highlights of Prescribing information and Full Prescribing Information, the abbreviation (b) (4) is utilized. This abbreviation is listed on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations. We recommend replacing the dose designations (b) (4), with 'mcg' or spell out 'microgram' throughout the insert labeling.
2. We recommend removing the (b) (4) because they are not properly titled and are confusing given the numerical similarity in the doses and volumes for injection provided. Additionally, we recommend revising this section with clearer directions for how to dilute phenylephrine to create a 100 mcg/mL solution for bolus intravenous administration.
3. We note that the currently proposed dosage and administration section of the insert labeling does not provide (b) (4). There are also no (b) (4). We recommend this information be included in the insert labeling by the Applicant as an additional subsection under Section 2 (i.e. following section 2.2, add this information as section 2.3).
4. Per consultation with ONDQA, the strength designation of (b) (4) is not necessary and should be removed from the labels and labeling; therefore, we recommend removing the (b) (4), throughout the insert labeling.

5.2 COMMENTS TO THE APPLICANT

A. Container Label for 10 mg/mL vial

1. Decrease the prominence of the net quantity statement '1 mL' by decreasing the font size so it does not compete with the prominence of the statement of strength.
2. The (b) (4) around the established name 'Phenylephrine HCl injection' intervenes between the name and the strength. Remove the (b) (4).
3. Remove (b) (4) from the strength statement in accordance with the USP monograph. Per email correspondence on June 19, 2012 with the ONDQA Chemist, the (b) (4) concentration symbol may be removed. The United States Pharmacopia (USP) lists the concentration for Phenylephrine Hydrochloride Injection as 10 mg/mL.
4. Revise 'For (b) (4) Use Only' to read 'For Intravenous Use'.

5. Ensure the established name and strength statement are the most prominent information on the label.
 6. Remove the (b) (4) statement from the label to minimize clutter and allow room for increasing the prominence of the established name and strength statements.
 7. Relocate the (b) (4) statement to appear under the 'Single Dose Vial' statement.
- B. Carton Labeling
1. See comments A1 through A5 above.
 2. Replace the hyphen symbol '-' with the word 'to' for the storage statement on the side display panel for increase clarity.
 3. Debold the 'Rx Only' statement to decrease its prominence.
 4. Relocate the 'Discard Unused Portion' statement to appear under the '25 x 1 mL Single Dose Vials' statement.

If you have further questions or need clarifications, please contact Cherye Milburn, project manager, at 301-796-2084.

APPENDICES

APPENDIX A: DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

ISMP DATABASES

QUANTROS MEDMARX DATABASE

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Appendix D: ISR numbers for the medication error cases identified in AERS

5972720
7610254
7493352
5633133
4182321
6943401
678468
6971442
5874298
7339906
8194083
3443839
7577760
1750528

Appendix E: Relevant AERS Cases

ISR # / Received Date	Narrative	Type of Error	Cause of Error	Outcomes
678468 19-Jul-90 Domestic	A 51 year old male status post carotid endarterectomy for right carotid stenosis was admitted to the ICU after receiving an overdose of 60 mg phenylephrine 1% via iv push followed by an additional 70 mg 45 minutes later. The patient's blood pressure rose to 220/120 and he developed pulmonary edema, hypotension, and ventricular bigeminy. He was successfully treated and discharged 5 days later. Myocardial enzyme elevation suggested myocardial injury.	Overdose of Phenylephrine	Not reported	Blood pressure rose to 220/120, pulmonary edema, hypotension, ventricular bigeminy. Myocardial enzyme elevation suggested myocardial injury
5633133 21-Feb-08 Domestic	This is a spontaneous report by a consumer (patient's wife) from the USA of accidental overdose, blood pressure increased, then blood pressure dropped, body feeling hot, chest pains, sweating, weakness and could not talk in a 65 year old Asian male patient subsequent to receiving phenylephrine hydrochloride therapy. On (b) (6) the patient received phenylephrine hydrochloride (dosage, route and indication unknown) during a stent procedure. According to the wife, the patient's blood pressure increased to "263" for 2-3 minutes and then dropped. The patient complained of his body feeling hot, chest pains, sweating, weakness and could not talk. Action taken with the phenylephrine hydrochloride was not known. The patient was treated with "Midoti" per the wife. The patient remained in the hospital and was discharged to home on (b) (6) with events resolved. It was not reported whether the events caused the hospitalization or prolonged his hospitalization. (b) (4) conservatively considered the events to be medically significant. The wife felt the events were possibly related to the phenylephrine. Further information was not available. The wife was queried for additional information. FOLLOW UP INFORMATION (15Feb2008): Patient demographics, medical history, concomitant medications, additional event details and outcome were added or	Overdose of Phenylephrine	Not reported	Patient's blood pressure increased to "263" for 2-3 minutes and then dropped. The patient complained of his body feeling hot, chest pains, sweating, weakness and could not talk. Prolonged hospitalization.

ISR # / Received Date	Narrative	Type of Error	Cause of Error	Outcomes
	<p>revised. On (b) (6), the patient underwent an elective angioplasty for stent placement for 90% blockage to his right coronary artery. The physician ordered 50 mcg of phenylephrine during the stent placement and the nurse mistakenly gave 10 mg of phenylephrine, however, it was not realized that an overdose had occurred until later. Almost immediately, the patient's blood pressure increased to 265 systolic and the patient experienced feeling hot, chest pain, sweating, weakness and could not talk. No treatment was provided. The patient's blood pressure dropped to 80 mmHg within 20-30 minutes and the other symptoms resolved. A phenylephrine drip was then started to titrate to maintain the blood pressure around 108 systolic. The patient recovered and was discharged to home on (b) (6). The wife was concerned because the patient's blood pressure remained "high" following discharge from the hospital. The reporter felt the events were related to the phenylephrine therapy. Medical history was significant for hypertension and coronary artery disease. Concomitant medications included Norvasc, Plavix and aspirin.</p>			
<p>5874298 8-Sep-08 Domestic</p>	<p>This is a spontaneous report by a pharmacist in the USA of medication error in a patient (age and gender not reported) after receiving phenylephrine ((10mg/mL) instead of metoclopramide (10mg/2mL). In Jul2008, the patient received 1 mL phenylephrine intravenously for an unknown indication. The intended drug was metoclopramide. Unspecified medical intervention was required to counter act the effect of phenylephrine and a cardiac consult was called. The reporter stated the "issue was resolved." The patient's medical history and concomitant medications were not reported. The reporter stated the error occurred because the cap colors and labels are similar. The cap color is white on both medications. The phenylephrine label is white with fuchsia or hot pink lettering for drug name and white</p>	<p>Wrong drug</p>	<p>Cap color similar, however different PDP was noted.</p>	<p>Cardiac consult was called</p>

ISR # / Received Date	Narrative	Type of Error	Cause of Error	Outcomes
	lettering on a navy blue background; the metoclopramide label is white with white lettering on a grape colored background for drug name and white lettering on a navy blue background for dosage.			
3443839 14-Jan-00 Domestic	90/73 headache, decreased fetal heart tones, hypertension, tingling ("nubain") 31 year old female presented for routine vaginal delivery (b)(6) She was given nubain 10mg x 2 on (b)(6) After the second med at 0800 (noted in chart as nubain) she had tingling in fingers, headache, BP 176/112, decrease in fetal heart tones to 60s. She was given Benadryl for "drug reaction" and immediately taken for cesarean section of live birth at 0816. Concomitant meds: oxytocin (probable, preventable, msv 3) msv reviewed last month indicated this patient received 10mg phenylephrine in error instead of nubain.	Wrong Drug	Not reported	Headache, decreased fetal heart tone, hypertension, cesarean section

Appendix F: NCC MERP Taxonomy

Category A: Circumstances or events that have the capacity to cause error.

Category B: An error occurred but the error did not reach the patient.

Category C: An error occurred that reached the patient, but did not cause patient harm.

Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G: An error occurred that may have contributed to or resulted in permanent patient harm.

Category H: An error occurred that required intervention necessary to sustain life.

Category I: An error occurred that may have contributed to or resulted in the patient's death.

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/s/

IRENE Z CHAN on behalf of FOREST R FORD
10/12/2012

IRENE Z CHAN
10/12/2012

SCOTT M DALLAS
10/12/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 11, 2012

To: Quynh Nguyen
Regulatory Project Manager
Division of Cardio-Renal Products (DCRP)

From: Emily Baker, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: **Phenylephrine HCl Injection
NDA 203826**

DPDP has reviewed the proposed Package Insert (PI) submitted for consult on March 9, 2012, for Phenylephrine HCl Injection. Our comments are based on the proposed labeling at the following EDR location: <\\CDSESUB1\EVSPROD\NDA203826\203826.enx>

The following comments, using the proposed PI posted in the e-room on October 10, 2012, by Quynh Nguyen, are provided directly on the attached, marked-up version of the label. DPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on the proposed materials.

If you have any questions on the comments for the PI or carton and container labeling, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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/s/

EMILY K BAKER
10/11/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Provision of Pharmacovigilance Data

Date: June 21, 2012

Reviewer(s): Eileen Wu, Safety Evaluator, PharmD
Division of Pharmacovigilance-1 (DPV-1)

Team Leader(s): Susan Lu, RPh
Division of Pharmacovigilance-1 (DPV-1)

Product Name(s): Phenylephrine HCl

Subject: All Adverse Events

Application Type/Number: 505(b)(2) NDA/ 203826

Applicant/Sponsor: West-Ward Pharmaceutical Corporation

OSE RCM #: 2012-1421

1 INTRODUCTION

On June 7, 2012, the Division of Cardiovascular and Renal Products requested a search of the Adverse Event Reporting System (AERS) and Empirica Signal databases for an overview of postmarketing adverse event reporting with intravenous phenylephrine HCl. This information was requested in support of an NDA review.

2 METHODS AND MATERIALS

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1.^a

Table 1. AERS Search Strategy	
Date of search	June 8, 2012
Time period of search	All dates up to June 8, 2012
Product Terms	Phenylephrine, Phenylephrine hydrochloride
MedDRA Search Terms	All reports
Other criteria	Route of Administration: intravenous

The Empirica Signal database was searched with the strategy described in Table 2.^b

Table 2. Data Mining Search Strategy	
Data Refresh Date	May 29, 2012
Product Terms	Phenylephrine IV (Custom Term)
Empirica Signal Run Name	7809 Phenylephrine iv without restrictions
MedDRA Search Strategy	All reports
Advanced Criteria	Subset 1968..1980-2012

3 DATA

^a AERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. AERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

^b OSE uses Empirica Signal software, which uses the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm, to perform analyses on AERS data and identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. MGPS analyzes the records in AERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on AERS data, limitations relating to AERS data also apply to data mining-derived data.

As of June 8, 2012, the AERS database contained 148 reports (crude counts) with phenylephrine intravenous formulation use. Seventy-eight reports had serious outcomes that included death (n= 20), life-threatening (n= 24), and hospitalization (n= 34).

Table 3 lists AERS crude counts of Preferred Terms reported for intravenous phenylephrine. Preferred terms with N >3 are sorted by decreasing number.

Table 3. AERS Crude Counts of Preferred Terms (N>3) for IV Phenylephrine as of June 8, 2012			
System Organ Class	Preferred Term	Count of PT (N)	Appears in the Draft Label *
Vascular disorders	Hypotension	20	
Vascular disorders	Hypertension	19	yes
Respiratory, thoracic and mediastinal disorders	Pulmonary edema	13	yes
General disorders and administration site conditions	Drug ineffective	9	
Respiratory, thoracic and mediastinal disorders	Lung infiltration	9	
Cardiac disorders	Bradycardia	8	yes
Injury, poisoning and procedural complications	Medication error	8	
Cardiac disorders	Tachycardia	8	yes (ventricular tachycardia)
Metabolism and nutrition disorders	Acidosis	7	
Nervous system disorders	Aphasia	7	
Nervous system disorders	Encephalopathy	6	
Metabolism and nutrition disorders	Lactic acidosis	6	
Injury, poisoning and procedural complications	Maternal exposure during pregnancy	6	
Cardiac disorders	Stress cardiomyopathy	6	
Cardiac disorders	Cardiac arrest	5	
Cardiac disorders	Cardio-respiratory arrest	5	
Psychiatric disorders	Delirium	5	
Investigations	Electrocardiogram ST segment elevation	5	yes (arrhythmia)
Injury, poisoning and procedural complications	Incorrect route of drug administration	5	
Skin and subcutaneous tissue disorders	Blister	4	
General disorders and administration	Necrosis	5	yes (skin necrosis)

System Organ Class	Preferred Term	Count of PT (N)	Appears in the Draft Label *
site conditions			
Cardiac disorders	Sinus tachycardia	5	yes (arrhythmia)
Nervous system disorders	Syncope	5	
Nervous system disorders	Unresponsive to stimuli	5	
Cardiac disorders	Arteriospasm coronary	4	
Psychiatric disorders	Anxiety	4	
Psychiatric disorders	Confusional state	4	
Investigations	Blood lactic acid increased	4	
Investigations	Blood pressure decreased	4	
Investigations	Blood pressure systolic increased	4	yes (hypertension)
Investigations	Electrocardiogram T wave inversion	4	yes (arrhythmia)
Skin and subcutaneous tissue disorders	Hyperhidrosis	4	
Metabolism and nutrition disorders	Metabolic acidosis	4	
Psychiatric disorders	Mental status changes	4	
Gastrointestinal disorders	Nausea	4	yes
Injury, poisoning and procedural complications	Procedural complication	4	
Metabolism and nutrition disorders	Propofol infusion syndrome	4	
Skin and subcutaneous tissue disorders	Rash erythematous	4	
Renal and urinary disorders	Renal failure	4	

* Phenylephrine Hydrochloride Injection, USP, 1 mg/mL, 1 mL Vial. 1.14.1.3 Draft Package Insert – Content of Labeling. Annotated Draft Phenylephrine Hydrochloride Injection, USP Package Insert in PLR format. West-Ward Pharmaceuticals, Eatontown, NJ 07724 USA. Revised December 2011 April, 2012. Amendment (Information request) submitted to FDA April 27, 2012.

Table 4. Lists drug event pairs with intravenous phenylephrine with an EB05 score >2.

Preferred term	N	EB05	EBGM	EB95
Stress cardiomyopathy	5	36.391	83.546	170.198
Propofol infusion syndrome	4	24.215	67.822	157.182
Lung infiltration	9	23.911	43.328	73.569
Acidosis	7	21.237	42.365	77.532
Lactic acidosis	6	5.643	24.463	52.716

Preferred term	N	EB05	EBGM	EB95
Arteriospasm coronary	4	5.512	43.211	110.662
Hypertension	16	4.169	7.086	12.701
Electrocardiogram T wave inversion	4	3.841	34.902	96.146
Hypotension	16	3.682	5.89	9.86
Pulmonary oedema	8	3.511	10.146	24.852
Electrocardiogram ST segment elevation	4	3.056	27.259	83.025
Tachycardia	10	2.781	4.993	9.625
Bradycardia	8	2.754	5.96	15.818
Blood pressure systolic increased	4	2.06	12.323	54.177

Table 5 lists AERS ISR numbers, AERS Case numbers, and Manufacturer Control numbers for the 148 reports with phenylephrine intravenous formulation.

ISR Number	Case Number	Manufacturer Control Number
423350	4510521	191686784
607107	4671692	13573
1542513	5198869	37722
1542665	5199015	37724
4059804	3910247	03H-153-0210305-00
4326936	4115849	FR-ROCHE-363060
4951698	6014069	CTU 272514
5369808	6342030	US-BAXTER-2007BH005675
3447044	6466771	
5874298	6750884	US-BAXTER-2008BH009197
5972720	6783918	GXKR2008CA08958
5999704	6850418	US-ASTRAZENECA-2008AC03133
6326363	7101952	20090370
6971039	7576524	US-BAXTER-2010BH022568
7222605	7757714	US-BAXTER-2011BH000236
7233149	7765336	NO-BAXTER-2011BH001296
7339906	7874068	821044
8423356	8605749	GB-TEVA-340755ISR
882022	4916008	8901449
3754877	3680813	
4361748	4144640	CTU 218955
4599815	5757608	141435USA
4652351	5788081	GB-GLAXOSMITHKLINE-B0379626A
4627201	5778415	5043
6003028	6777921	2008-183378-NL
5916976	6786149	AT-BAUSCH-2008BL004282
5972732	6783969	GXKR2008CA08956
5152186	6901514	CA-GLAXOSMITHKLINE-B0446335A
6128576	6948967	JP-ROXANE LABORATORIES, INC.-2009-RO-00244RO
6199499	6993411	US-AVENTIS-200817519US

Table 5. AERS ISR Numbers, AERS Case Numbers and Manufacturer Control Numbers for the 148 Reports with Phenylephrine Intravenous Formulation as of June 8, 2012

ISR Number	Case Number	Manufacturer Control Number
7619630	7193422	US-BAYER-200940878NA
6468148	7197685	GB-BAUSCH-2009BL006226
6700273	7368870	US-BAXTER-2010BH010529
6700281	7368878	US-BAXTER-2010BH010589
6700285	7368882	US-BAXTER-2010BH010594
6662151	7339865	US-BAXTER-2010BH008108
7232843	7442971	NO-BAXTER-2010BH016546
7687231	8092943	US-BAUSCH-2011BL005358
7579766	8040375	950649
7899036	8197090	FR-ASTRAZENECA-2011SE62766
1542779	5199124	37723
921550	4951429	
917442	4947778	9201371
4495805	5673565	20041000433
4664346	5798059	2005GB00878
4978144	6035360	06H-163-0307243-00
5399686	6369437	GB-BAUSCH-2007BL002375
5534683	6481276	US-BAXTER-2007BH009448
5781601	6675025	US-TEVA-173008USA
5993326	6844430	US-ASTRAZENECA-2008AC03135
6485904	7223756	443138
6700275	7368872	US-BAXTER-2010BH010582
6700276	7368873	US-BAXTER-2010BH010583
7231865	7764342	-VALEANT-2011VX000002
7610254	7975279	2011SP021439
7584023	8030032	953540
8168131	8428991	DE-ASTRAZENECA-2012SE11912
583906	4651248	
1924474	5568349	
788915	4832837	101091313A
4831669	5929436	200513809GDS
4900773	5985329	06H-167-0304607-00
3458517	6158454	2000AP00588
5301270	6301530	2007-00775
5865795	6743637	US-ASTRAZENECA-2008AC02238
5972721	6783965	GXKR2008CA08957
6279694	6967633	IE-ROXANE LABORATORIES, INC.-2009-RO-00343RO
6700274	7368871	US-BAXTER-2010BH010580
6700278	7368875	US-BAXTER-2010BH010585
6700282	7368879	US-BAXTER-2010BH010590
6700284	7368881	US-BAXTER-2010BH010592
6700286	7368883	US-BAXTER-2010BH010595
6334444	7293313	355738
6943401	7555212	US-ROXANE LABORATORIES, INC.-2010-RO-01119RO
6965797	7572950	FR-ROCHE-724269

Table 5. AERS ISR Numbers, AERS Case Numbers and Manufacturer Control Numbers for the 148 Reports with Phenylephrine Intravenous Formulation as of June 8, 2012

ISR Number	Case Number	Manufacturer Control Number
7105350	7873710	JHP201000335
7376673	7884329	GER/USA/11/0017688
7493352	7971524	CTU 454102
8151364	7966775	FR-BAXTER-2011BH017150
8194083	8447930	FR-VALEANT-2012VX000777
678468	4734302	14325
1542667	5199017	37725
1489537	5148663	
3443839	3417806	
4329658	4091514	PHRM2004FR00768
5015671	6061510	2006BH010040
5426351	6427773	US-BAXTER-2007BH006999
5806197	6704150	CTU 342813
5535196	6689419	ES-JNJFOC-20071108898
6248047	7035163	IN-BAUSCH-2009BL003088
6390401	7147069	CTU 394080
6700280	7368877	US-BAXTER-2010BH010588
7085575	7657887	US-BAYER-201044124GPV
7407087	7894055	IN-BAUSCH-2011BL002168
7745782	7989667	2011SP023020
7577760	8012831	FR-VALEANT-2011VX000050
1578221	5232987	WAES95020016
1419260	5083174	
1750528	5399682	96001621
3942459	3813949	CTU 171328
4303557	4100458	401025410
4257391	4056552	2003-109738-NL
5118899	6132015	2006-147270-NL
5633133	6550738	US-BAXTER-2008BH001154
6255623	7040681	GB-BAUSCH-2009BL003132
6161679	6986562	2009-1
6187922	6996277	CTU 376575
6313368	7084490	US-ROXANE LABORATORIES, INC.-2009-RO-00827RO
6338380	7110729	2009EK003929
6700283	7368880	US-BAXTER-2010BH010591
6701528	7370444	JHP201000126
6971442	7518824	US-BAXTER-2010BH019785
7290838	7466188	NO-ASTRAZENECA-2010SE31893
7234118	7766076	GB-VALEANT-2010VX002223
8245336	8470282	GR-ABBOTT-12P-066-0916309-00
8326755	8539184	JP-JHP PHARMACEUTICALS, LLC-JHP201200231
8175973	8446214	FK201101078
88502	4312858	
1734198	5383724	
4182321	3999873	03H-163-0230260-00

Table 5. AERS ISR Numbers, AERS Case Numbers and Manufacturer Control Numbers for the 148 Reports with Phenylephrine Intravenous Formulation as of June 8, 2012

ISR Number	Case Number	Manufacturer Control Number
4433065	4113327	2004AC00007
4746729	5862257	GB-GLAXOSMITHKLINE-B0390253A
4981092	6028271	06H-163-0306917-00
5915359	6784667	US-BAUSCH-2008BL004171
6012187	6856516	US-ASTRAZENECA-2008AC03134
6337559	7103080	US-TEVA-207744USA
6327448	7095905	US-PURDUE-USA-2009-0039693
6672669	7360978	20100127
6700279	7368876	US-BAXTER-2010BH010587
6608938	7300860	US-ROXANE LABORATORIES, INC.-2010-RO-00203RO
6716393	7381243	US-ROXANE LABORATORIES, INC.-2010-RO-00526RO
6972592	7577556	FR-ASTRAZENECA-2010SE41342
7167850	7715080	IN-BAUSCH-2010BL006841
8181972	8381432	JP-ABBOTT-11P-087-0874640-00
1417772	5081813	U018440
1525990	5183136	M047720
1530349	5187283	36763
1542785	5199128	37721
1700720	5351081	95080226
569069	4638326	
1890934	5535769	
3178746	3191497	
4009619	3865462	02H-143-0203035-00
4235137	4035815	M1301-2003
4300868	4127896	J400925410
6329866	7097667	US-BAXTER-2009BH013016
6700277	7368874	US-BAXTER-2010BH010584
7026787	7632694	2010P1001494

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/s/

EILEEN WU
06/21/2012

SUSAN LU
06/21/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 203-826 BLA#	NDA Supplement #:S- BLA Supplement #
Efficacy Supplement Type SE-	
Proprietary Name: Established/Proper Name: Phenylephrine HCl Dosage Form: Injection Strengths: 10 mg/mL	
Applicant: West-Ward Pharmaceutical Corp. Agent for Applicant (if applicable):	
Date of Application: 12-27-11 Date of Receipt: 12-28-12 Date clock started after UN: 1-12-12	
PDUFA Goal Date: 11-12-12	Action Goal Date (if different): 11-9-12
Filing Date: 3-12-12	Date of Filing Meeting: 2-27-12
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7	
Proposed indication(s)/Proposed change(s): Increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): Pre-IND 109,977				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			UN'ed on 1-11-12; Rec'd User Fee on 1-12-12

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		<p>No RLD is listed in the Orange Book.</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: Sponsor did not request # years.</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	Paragraph I certification submitted.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?			X	This NDA is based solely on the literature.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?			X	This NDA is based solely on the

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				literature.
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	This is an electronic submission.

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11-10-10 <i>If yes, distribute minutes before filing meeting</i>	X			Pre-NDA Meeting held with Baxter on 11-10-10 under P-IND 109977.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-27-12

BLA/NDA/Supp #: NDA 203-826

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Phenylephrine HCl

DOSAGE FORM/STRENGTH: Injection, 10 mg/mL

APPLICANT: West-Ward Pharmaceutical Corp.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.

BACKGROUND: West-Ward Pharmaceutical Corp. submitted this 505(b)(2) NDA for Phenylephrine HCl Injection, USP, 10 mg/mL, a vasoconstrictor and pressor drug. The proposed indication is to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension. In support of approval, the sponsor intends to rely solely on the published literature for the non-clinical profile, clinical pharmacology, clinical safety and efficacy of the proposed drug product.

There is currently no listing of a Reference Listed Drug in the Orange Book for Phenylephrine HCl Injection and the sponsor has submitted a Paragraph I certification. According to the sponsor, the drug product has historically been marketed under the “Grandfather” exemption and the NDA was submitted to comply with the “Marketed Unapproved Drugs – Compliance Policy Guide” Sec. 440.100 Guidance.

A Pre-NDA Meeting was held on November 10, 2010 with Baxter, the holder of Pre-IND 109,977 at the time.

This NDA was submitted in electronic format using the eCTD specifications.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Shari Targum	Y
	TL:	Shari Targum	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sudharshan Hariharan	Y
	TL:	Rajnikanth Madabushi	Y
Biostatistics	Reviewer:	Cherry Liu	Y
	TL:	James Hung	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Phil Gatti	Y
	TL:	Albert Defelice	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wendy Wilson-Lee	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erica Pfeiler	Y
	TL:	Bryan Riley	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	TBD	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Janice Pohlman	Y
	TL:	Susan Thompson	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Stephen Grant (DCRP); Nina Ton, Susan Lu (OSE); Sally Loewke (OND); Kim-Chi Simmons (OC)		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: This NDA is based solely on the literature.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: This is a 505(b)(2) NDA.</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Micro comments to be included in Day 74 Letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Division</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Pediatric data may not be sufficient to fulfill PREA requirements.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Quynh Nguyen, PharmD, RAC

2-27-12

Regulatory Project Manager

Date

Edward Fromm, RPh, RAC

2-27-12

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

QUYNH M NGUYEN
04/18/2012