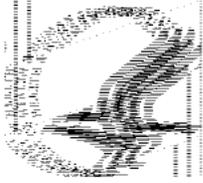


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204485Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Pediatric and Maternal Health Staff Review

Date: May 23, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Pitressin[®] (vasopressin, injection, USP)

NDA: 204-485

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Applicant: JHP Pharmaceuticals, LLC.

Materials Reviewed: Pitressin labeling, submitted February 1, 2013.

Consult Question: “Please review and provide edits to the proposed Content of Labeling for the following section: 8.3 PREGNANCY.”

INTRODUCTION

On September 25, 2012, JHP Pharmaceuticals, LLC., submitted a 505(b)(2) New Drug Application for Pitressin (vasopressin) Injection, a marketed unapproved drug, for the proposed indication of vasodilatory shock (including post-cardiotomy shock and septic shock). In a Pre-IND (PIND 112,944) meeting between the sponsor and the Division of Cardiovascular and Renal Products (DCRP) on October 17, 2011, the DCRP agreed that it was acceptable for the sponsor to provide a literature-based review for the proposed indication given the extensive clinical experience with the product over several decades.

The Division of Cardiovascular and Renal Products (DCRP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Pitressin labeling.

This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Pitressin (vasopressin, injection, USP) is a synthetic version of vasopressin identical to the natural peptide produced in the posterior pituitary gland. Pitressin is available as an intravenous solution at a concentration of 20 pressor units/mL, and contains the preservative chlorobutanol (a chloroform derivative). This product (manufactured by JHP Pharmaceuticals) is the same product originally marketed by Parke-Davis. Pitressin is a pre-1938 drug product that has never received FDA approval, but has been marketed for almost 100 years. In June 2006, FDA announced a new drug safety initiative to remove unapproved drugs from the market, and issued a final guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide (CPG)," outlining its enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process. This application, NDA 204-485, is the first Pitressin product seeking FDA approval.

The natural peptide vasopressin, also known as antidiuretic hormone, is stored in the posterior pituitary in mammals and secreted by the hypothalamus. Its primary role in the body is to regulate serum osmolality and vascular tone.¹ Vasopressin stimulates the renal vasopressin V2 receptors which are coupled to adenylyl cyclase and cyclic AMP which causes increased water permeability at the luminal surface of the distal convoluted tubule and collecting duct, leading to increased free water reabsorption and resulting in increased urine osmolality and decreased urinary flow. In addition, vasopressin directly stimulates contraction of smooth muscle V1 receptors which mediates its vasoconstrictive effects.¹

Role of naturally occurring vasopressin in pregnancy

Systemic arterial vasodilation occurs early in the first trimester prior to the maturation of the placenta.² Arterial vasodilation early in pregnancy is believed to be associated with a decline in plasma osmolality and an increase in thirst and increase in water intake stimulating the release of

¹ McEvoy, Gerald, et al. "Vasopressin." *AHFS Drug Information*. 2012. *Stat!Ref*. Web. 1 May 2013.

² Schrier, Robert W. *J Am Soc Nephrol*. Systemic Arterial Vasodilation, Vasopressin and Vasopressinase in Pregnancy. 21:570-572, 2010

vasopressin. Vasopressinase, a cystine aminopeptidase produced by the trophoblasts of the placenta enhances the clearance of vasopressin. Vasopressinase levels increase four-fold during the middle and late stages of pregnancy, thus increasing the clearance of vasopressin. vasopressin levels return to normal approximately 3 months postpartum.²

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Studies have not been conducted with Pitressin in pregnant woman or in animals; hence, the pregnancy category C designation (see 22 CFR 201.57(c)(9)(i)(3)). Clinical Pharmacology updated the Dosing and Administration and the Clinical Pharmacology sections of Pitressin labeling with dosing and pharmacokinetic information from a review of published literature. Appropriate cross-references were placed in the pregnancy subsection of Pitressin labeling.

The Drugs and Lactation Database (LactMed)³ was searched for available lactation data on with the use of Pitressin or vasopressin, and no information was located. Hale (2006)⁴ reported that although vasopressin is probably present in human milk, it is rapidly destroyed in the gastrointestinal tract, and systemic absorption through breast milk feeding is unlikely. Alternatively, a lactating woman may choose to pump and discard breast milk for 5 half-lives after administration of Pitressin (approximately 1.5 hours) in order to avoid any exposure to an infant through breast milk. Drugs, with the exception of radiopharmaceuticals, are considered eliminated from the systemic circulation between 4 to 5 half-lives.

CONCLUSION

The pregnancy subsection of Pitressin labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of Pitressin labeling was revised to comply with current labeling recommendations.

³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

⁴ Hale, T. Medications and Mothers Milk, 12th ed. Hale Publishing, 2006

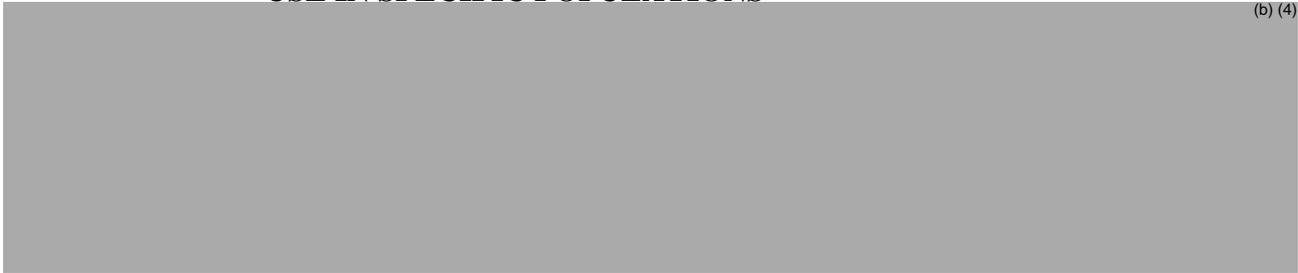
The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on May 9, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----**USE IN SPECIFIC POPULATIONS**-----



Reviewer comment: As noted in the Label Review Tool from SEALD, pregnancy category should not be in the highlights of prescribing information section. In addition, clinical pharmacology will update Dosing and Administration under Highlights.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C



Risk Summary

There are no adequate or well-controlled studies of (b) (4) in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin.

Clinical Considerations

(b) (4)

(b) (4) (b) (4) (b) (4)
contractions that could threaten the continuation a pregnancy (b) (4)

(b) (4)

(b) (4)

(b) (4)

8.3 Nursing Mothers

(b) (4)

It is not known whether (b) (4) is present in human milk. However, oral absorption of (b) (4) by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. A lactating woman may choose to pump and discard breast milk for 1.5 hours after receiving (b) (4) to minimize potential exposure to the breastfed infant. Caution should be exercised when (b) (4) is administered to a nursing woman

17 PATIENT COUNSELING INFORMATION

This section did not receive any edits from PMHS-MHT as this product is only used under the supervision of a physician.

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

/s/

CARRIE M CERESA
05/23/2013

JEANINE A BEST
05/23/2013

LYNNE P YAO
05/24/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 204-485	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Vasostrict Established/Proper Name: vasopressin, USP Dosage Form: Injection Strengths: 20 units per mL		
Applicant: Par Sterile Products, LLC		
Date of Receipt: 9-26-12 (Re-submission date is 10-18-13)		
PDUFA Goal Date: 4-18-14		Action Goal Date (if different):
RPM: Quynh Nguyen, Pharm.D., RAC		
Proposed Indication(s): Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.		

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Non-clinical, clinical pharmacology, clinical safety and efficacy data

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 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)

Applicant has provided evidence of in-vivo bioavailability using the published literature.

Comparison of the proposed drug product formulation to those formulations used in the published literature, indicate that the formulation and concentration of vasopressin for each one of the products used in these references is not significantly different from that of the proposed product. The differences in the drug products are not expected to affect the bioavailability of vasopressin via the IV route of administration.

See 21 CFR 320.24(b)(6).

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).

Pitressin

(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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	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 final OTC drug monograph?

YES NO

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

Name of drug(s) described in a final OTC drug 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: Pitressin tannate (in oil)

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").

This application provides for a new indication and change in dosage form. The dosage form is changing from a sterile suspension for intramuscular administration for NDA 3402, Pitressin Tannate in Oil, to a sterile, aqueous solution for intravenous administration.

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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

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?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
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)?
N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
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):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(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

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
04/17/2014

RHPM Overview – AP Action
NDA 204-485
Vasopressin (vasopressin injection, USP)
20 units per mL

Sponsor: Par Sterile Products, LLC (formerly JHP Pharmaceuticals, LLC)
Classification: Standard
Letter Date: September 25, 2012
User Fee Receipt Date: September 26, 2012
User Fee Goal Date: July 26, 2013
Complete Response Action: July 19, 2013
Resubmission Receipt Date: October 18, 2013
User Fee Goal Date: April 18, 2014

Background

Please refer to my **RPM Overview – CR Action** dated July 19, 2013 in DARRTS for the regulatory history and summary of previous cycle reviews that led to the Complete Response (CR) Letter dated July 19, 2013.

The July 19, 2013 CR Letter contained the following deficiencies/comments:

Product Quality

Twenty CMC-related comments, including 6 comments regarding Drug Substance and 14 comments regarding Drug Product (see CR Letter in DARRTS for the comments).

Clinical Pharmacology

Stability of AVP in diluents other than isosaline and dextrose

The diluent used for diluting AVP prior to infusion is not stated in most of the publications reporting on clinical trials. The stability of AVP was tested by the sponsor in only 2 diluents: isosaline and 5% dextrose. AVP was found to be stable in isosaline. However, when dissolved in 5% dextrose AVP was unstable. The reason for the instability of AVP in 5% dextrose is not known. There is a need to determine the stability of AVP in additional diluents such as, Ringer's, lactated Ringer's, sodium citrate and Plasma-Lyte® in order to exclude the possibility that degradation of AVP occurred in the published trials that did not state the diluents used.

REQUIRED PEDIATRIC ASSESSMENTS

As described in our LABELING PMR/PMC DISCUSSION COMMENTS Letter dated June 26, 2013:

We note that you have requested in your March 6, 2013 submission a full Pediatric Waiver from the requirement for pediatric studies under Section 505B(a)(4)(A) of the Act. However, we believe that additional data in pediatric patients are required. These data may be obtained post-approval as part of a Postmarketing Requirement (PMR) in which you commit to attempt to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in your submission (e.g., Choong et. al. [2009]). We would need to reach agreement on this PMR before the application can be approved.

Refer to the *Guidance for Industry: How to Comply with the Pediatric Research Equity Act* (September 2005) and submit a pediatric plan to support the deferral of pediatric studies. Your pediatric plan must include the submission date(s) for the pediatric study information you plan to supply.

SAFETY UPDATE

See CR Letter in DARRTS for the language requesting a safety update.

The applicant submitted a response to the CR Letter on October 18, 2013. The resubmission contained a response to the comments regarding Product Quality, Clinical Pharmacology, Required Pediatric Assessments, and Safety Update. In addition, the resubmission contained a response to the labeling comments in the LABELING PMR/PMC DISCUSSION COMMENTS Letter dated June 26, 2013.

Upon review, it was determined that the resubmission and subsequent amendments address all the issues in the CR Letter and LABELING PMR/PMC DISCUSSION COMMENTS Letter as noted below.

Division Director's Memo

In his 4-4-14 review, Dr. Stockbridge wrote the following:

This memo conveys the Division's recommendation to issue an Approval letter for this application.

In the first cycle, the Division issued a Complete Response (19 July 2014), citing 20 product quality issues. The applicant's response (18 October 2013) was reviewed by CMC (Soldatova, 18 March 2014). There is a supplementary CDTL memo (Targum, 27 March 2014) with which I am in full agreement. I highlight a few matters here.

All CMC product quality issues have been resolved. In addition, the sponsor provided information supporting dilution in additional bulk parenteral products, and these are satisfactory.

At the recommendation of the PeRC, we asked the sponsor to look into the feasibility of acquiring data from a study conducted in children. The sponsor did contact the author, and Dr. Targum documents their attempt. She and I are satisfied.

The sole issue affecting approvability at this point is an outstanding facility inspection.

[RPM Note: The Office of Compliance issued an Overall Recommendation of "Acceptable" on 4-4-14; see Quality review dated 4-8-14.]

Cross-Discipline Team Leader (CDTL) Review

In her 3-27-14 review, Dr. Targum wrote the following:

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Pending acceptable labeling and Office of Compliance recommendation, I recommend approval of vasopressin to increase mean arterial pressure in adult patients with vasodilatory shock who remain hypotensive despite fluids and catecholamine pressors.

Clinical Review

Dr. Fiszman reviewed the applicant's Pediatric Study Plan submitted on December 23, 2013 and labeling response submitted on October 18, 2013. See DARRTS for Dr. Fiszman's review dated 2-21-14.

Quality Review

In Dr. Soldatova's 4-8-14 review, she wrote the following:

Recommendation and Conclusion on Approvability

NDA 204-485 for Vasostrict™ (vasopressin injection, USP), 20 units /ml, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the 12-month expiration dating period

is recommended for drug product stored in the proposed container/closure system at the recommended storage condition, between 15°C and 25°C (59°F and 77°F)". The overall Acceptable OC recommendation for drug substance and drug product facilities is issued on 04-Apr-2014.

See also Dr. Soldatova's Quality Review dated 3-18-14 in DARRTS.

[Note: The CR Letter included a Clinical Pharmacology comment on "Stability of AVP in diluents other than isosaline and dextrose." The applicant provided a response to this comment in their October 18, 2013 resubmission. Dr. Hinderling stated that he had no further comments on their response. Dr. Soldatova reviewed and addressed the applicant's response in her Quality Review dated 3-18-14.]

Product Quality Microbiology

In Dr. Pfeiler's 12-3-13 review, she wrote the following:

Post-dilution hold data for NDA 204485 in 5% Dextrose Injection USP, Lactated Ringer's USP, Plasma-Lyate A Injection USP, and Ringer's Injection USP, is adequate to support an 18 hour hold at room temperature and a 24 hour hold under refrigeration.

EER Report (Manufacturing Site Inspections)

The Office of Compliance issued an Overall Recommendation of "Acceptable" on 4-4-14; see Quality review dated 4-8-14.

Safety Update

Dr. Stockbridge reviewed the applicant's Safety Update submitted on 10-18-13 and he stated that there were no novel safety concerns based on the submission. This will be noted in the action letter.

Pediatrics

A PeRC meeting was held on 5-8-13. The PeRC disagreed with the Division's decision to grant the applicant's request for a full waiver. Instead, the PeRC recommended a postmarketing requirement (PMR) for the sponsor to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the Investigators of the published pediatric studies in this submission. This recommendation was included in the LABELING PMR/PMC DISCUSSION COMMENTS Letter dated 6-26-13 and CR Letter dated 7-17-13.

The applicant submitted a proposed Pediatric Study Plan (PSP) on 10-18-13 and a revised PSP on 12-23-13. The following is excerpted from Dr. Targum's 3-27-13 CDTL review:

In a December, 2013 pediatric study plan, the applicant documented that Dr. Choong was contacted. Dr. Choong offered to contact co-investigators to determine if they would be willing to seek Research Ethics Board approval to provide the requested information. However, informed consent forms did not authorize use of patient data to be provided to entities not specifically listed in the informed consent forms. Choong's study sponsor, a competitor (Fering, Inc.) would likely need to grant permission for the investigators to provide study data. Dr. Choong also offered to contact a number of pediatric cardiologists to determine their willingness to provide information on vasopressin use; however, the applicant did not receive a response to this inquiry. The applicant also proposed to conduct literature searches for the use of vasopressin in pediatric patients with vasodilatory shock, reporting relevant findings in the annual reports.

On February 6, 2014, the reviewers discussed the applicants proposed pediatric safety plan; in view of the obstacles encountered by the applicant, the reviewers decided to recommend granting a waiver for conducting studies in pediatric patients.

See also Dr. Fiszman's 2-21-14 Clinical review for additional information.

[Note: Per an 11-12-13 email from George Greeley, PeRC RPM: “Since the review has already occurred before the PeRC, there is no need for a follow-up review as the PeRC recommendations were offered for this application.”]

Labeling

The original submission contains proposed draft labeling for the package insert (PI) in PLR format, and container and carton labeling. No Patient PI (PPI) was submitted.

Labeling comments on the PI and carton and container were conveyed to the applicant in the LABELING PMR/PMC DISCUSSION COMMENTS Letter dated 6-26-13; the applicant submitted a response in their 10-18-13 resubmission.

DMEPA provided comments on the proposed revised carton and container labeling in reviews dated 4-8-14, 2-26-14, and 2-14-14.

The Division’s comments on the PI were sent to the applicant on 4-4-14, 3-21-14, and 3-5-14. The applicant submitted the agreed-upon PI on 4-14-14.

Proprietary name review

DMEPA found the proposed name “(b)(4)” unacceptable on 3-6-13 due to wrong medication errors seen with the drug, (b)(4). On 5-20-13, a request for proprietary name review was received for “(b)(4)” as the primary name with an alternate name of “VasoStrict.” A teleconference between DMEPA and the applicant was held on 6-12-13 to discuss the proposed alternate names. The alternate name “(b)(4)” was subsequently withdrawn on 6-24-13. On 11-18-13, the applicant submitted a request for review of the proposed proprietary name “Vasostrict.” The name “Vasostrict” was found to be acceptable by DMEPA on 2-6-14 (see DMEPA reviews and minutes of the 6-17-13 telecon in DARRTS).

Safety Discussion

In the previous review cycle, Drs. Fisman and Targum had indicated at the Wrap-up/Safety Meeting on 6-20-13 that there were no safety concerns that would preclude approval of the application.

At the Wrap-up/Safety Meeting on 3-5-14 for the resubmission, Dr. Targum indicated that there were no safety concerns.

Postmarketing Requirements/Commitments (PMR/PMC)

There is no PMR/PMC. The applicant has responded to the comments in our 6-26-13 LABELING PMR/PMC DISCUSSION COMMENTS Letter “to attempt to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in [their] submission (e.g., Choong et. al. [2009]).” See above under **Pediatrics**.

User Fee

The sponsor paid the user fee in full (User Fee ID# PD3012638).

505(b)(2) Clearance

Per a 3-20-14 email from Mary Ann Holovac of the OND IO, this NDA is cleared for action from a 505(b)(2) perspective.

RPM Summary

As all issues in the July 19, 2013 CR Letter and 6-26-13 LABELING PMR/PMC DISCUSSION COMMENTS Letter have been addressed, an AP Letter will be drafted for Dr. Stockbridge’s signature.

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
4-17-14

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
04/17/2014

LABEL AND LABELING MEMO

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date : April 8, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 204485
Product Name and Strength: Vasopressin (Vasopressin Injection, USP)
20 units per mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: JHP Pharmaceuticals
Submission Date: April 7, 2014
OSE RCM #: 2013-2864-2
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Lisa Khosla, PharmD, MHA

1 INTRODUCTION

This memorandum evaluates the revised container and carton labeling for Vasopressin (vasopressin injection, USP) submitted on April 7, 2014 (Appendix A).

2 MATERIAL REVIEWED

DMEPA reviewed the revised container label and carton labeling submitted on April 7, 2014. We compared the revised labels against the recommendations contained in OSE Review # 2013-2864 dated February 12, 2014 and OSE Review #2013-2864-1 dated February 26, 2014 for NDA 204485.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cheryle Milburn, at 301-796-2048.

1 Pages 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/

JANINE A STEWART
04/08/2014

LISA V KHOSLA
04/08/2014

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

Product Title¹	Vasostriect (vasopressin injection, USP) for intravenous use
Applicant	Par Pharmaceutical Companies
Application/Supplement Number	NDA 204485
Type of Application	Original
Indication(s)	Vasostriect is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
Office/Division	ODE I/DCRP
Division Project Manager	Quynh Nguyen
Date FDA Received Application	October 18, 2013
Goal Date	April 18, 2014
Date PI Received by SEALD	April 1, 2014
SEALD Review Date	April 3, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **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:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

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

Comment:

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

Instructions to complete this item: If the length of the HL is one-half page or less, 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 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” 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:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The headings for I&U, Contraindications, W&P, DI and USP are not centered.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment: Summarized statements in I&U, D&A (first paragraph), and DI do not have references. Also, for consistency, recommend adding a bullet before the first paragraph under D&A.

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• 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: It is assumed that, at this time, the review division does not believe that the Patient Counseling Information section is applicable given the indication for this drug and the Patient Counseling Information Statement, therefore, is not included in HL.

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The name of the drug is not in UPPER CASE and should be.

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

Selected Requirements of Prescribing Information

Approval:” followed by the **4-digit year**.

Comment: *The 4-digit year is missing and should read: "2014"*

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW 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 and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC 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 in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

Selected Requirements of Prescribing Information

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. 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 in Highlights

- N/A** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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 in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The date is missing and should read: "4/2013". Also, the revision date should be right justified, in line with the far right line of text.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment: Currently, the heading is on the first two lines of the left-sided column. See Appendix A for the recommended format (the heading goes across the top of TOC, taking up a single line).
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: The headings for subsections 7.5 and 7.6 are not in title case. The headings should read: "7.5 Drugs Suspected of Causing SIADH"; "7.6 Drugs Suspected of Causing Diabetes Insipidus". Subsection 12.1 should read: "Mechanism of Action" and currently reads "Mechanism of action".
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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: The words "full prescribing information" should be in lower case and currently is in title case "Full Prescribing Information".

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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
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: Under section 13 of the FPI there is a subheading: "Carcinogenesis, Mutagenesis, Impairment of Fertility"; this subheading should be replaced with the bolded numerical indicator (13.1) and subsection heading as indicated above (this will also affect TOC). Also, the heading for section 13 reads "NON-CLINICAL TOXICOLOGY"; the hyphen is not needed.

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed

Selected Requirements of Prescribing Information

within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

Comment: *In subsection 8.5, the cross-reference reads: “[see Warnings and Precautions (5), Adverse Reactions (6), and Drug-Drug Interactions (12.3)]”. The presentation should include the section so the last part of the cross-reference should read “.. and Clinical Pharmacology (12.3)”.*

- N/A** 34. 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

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW 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 and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are 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:

“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 practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are 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

Selected Requirements of Prescribing Information

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *This statement has been modified and is acceptable.*

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

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

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ELIZABETH A DONOHOE
04/03/2014

ERIC R BRODSKY
04/03/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

LABEL AND LABELING MEMO

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date : February 26, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 204485
Product Name and Strength: Vasopressin (vasopressin injection, USP) Synthetic
20 units per mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: JHP Pharmaceuticals
Submission Date: February 25, 2014
OSE RCM #: 2013-2864-1
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Lisa Khosla, PharmD, MHA

1 INTRODUCTION

This memorandum evaluates the revised carton and container labels for Vasopressin (vasopressin injection, USP) Synthetic 20 units per mL, NDA 204485, submitted on February 25, 2014 (Appendix A). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-2864 dated February 12, 2014.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels submitted on February 25, 2014. We compared the revised labels against the recommendations contained in OSE Review # 2013-2864 dated February 12, 2014.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cheryle Milburn, at 301-796-2048.

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

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/s/

JANINE A STEWART
02/26/2014

LISA V KHOSLA
02/27/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review: February 12, 2014
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 204485
Product Name and Strength: Vasostriect (vasopressin injection, USP) 20 units/mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: JHP Pharmaceuticals
Submission Date: December 23, 2013
November 18, 2013
OSE RCM #: 2013-2864
DMEPA Primary Reviewer: Janine Stewart, PharmD
DMEPA Team Leader: Lisa Khosla, PharmD, MHA

1. REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Vasopressin (Vasopressin Injection, USP), for areas of vulnerability that could lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP). DMEPA previously reviewed the label and labeling submitted by JHP Pharmaceuticals for NDA (b) (4) in OSE RCM# 2012-2808 dated June 7, 2013.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D- N/A
ISMP Newsletters	E
Regulatory History	F
Container Label, Carton Labeling, Full Prescribing Information	G

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Although no medication errors were identified that were relevant to this review, we performed a risk assessment of the proposed full prescribing information, container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note that the presentation of the established name and the strength statement on the container label and the carton labeling includes product information that is redundant. We also note that the information regarding the stability of the diluted solution for infusion as well as the proper storage of the product appears to be inconsistent between the carton and container labeling and the insert labeling. Additionally, we note the use of error prone abbreviations, and/or trailing zeros in dose designations in areas of the container label, carton labeling, and full prescribing information.

Moreover, we note that historically, vasopressin has been used through the intramuscular, subcutaneous, and intravenous routes of administration. However, for the proposed indication of vasodilatory shock (including post-cardiotomy shock or septic shock), vasopressin should

only be administered as an intravenous infusion. Due to the previous use of other routes of administration by healthcare practitioners, the intended route of intravenous infusion should be further supported by a statement that notifies the user that the solution must be further diluted prior to intravenous infusion. Therefore, we provide recommendations in Section 4 in order to promote the safe use of this product. Furthermore, we considered recommendations from OSE Review #2012-2808 and have reiterated them since they have not been implemented by the Applicant.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to approval of this NDA:

A. Insert Labeling:

1. The abbreviations “IV, U” and trailing zero can be found in the Dosage and Administration section of insert labeling for this product. We recommend replacing the abbreviation such as ‘U’ with the appropriate full meaning of ‘unit’ or the abbreviation such as ‘IV’ with the appropriate full meaning of ‘intravenous’. In addition, trailing zeros is also error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. ‘1.0’ can be misinterpreted as ‘10’); thus, we recommend removing the trailing zeros where they appear in the insert labeling.
2. Add the appropriate unit of measure to follow each corresponding number throughout the insert labeling (e.g., the units/minute in *Highlights of Prescribing Information* and °C and °F in the *How Supplied* section).
3. Replace the proprietary name ‘*VasoStrict*’ with ‘*Vasostrict*’ where it appears throughout the insert labeling. This is an example of tall-man (mixed-case or enlarged) lettering. Tall-man letters are used to emphasize the differing portions of two names in order to help differentiate them by drawing attention to their dissimilarities. It is typically used to differentiate known look-alike names that have been confused and resulted in wrong drug medication errors. Thus, the tall-man lettering in this proposed proprietary name is inappropriate and should not be used.

4. Revise Table 1 of Section 2, *Dosage and Administration* to reflect the equivalent number of units corresponding to the volume of Vasopressin required to prepare each infusion concentration. Additionally, revise the statement 'Final conc' to read 'Final Concentration' and add the units of measure to each numerical value in the table. Refer to the following example:

Fluid Restriction?	Final Concentration	Mix	
		Vasopressin [®]	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 units/mL	5 mL (100 units)	100 mL

4.2 RECOMMENDATIONS FOR THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA.

A. Container Labels

1. Ensure the established name "(Vasopressin Injection, USP) (b) (4)" is printed in letters that are at least ½ the size of letters comprising the proprietary name, and the established name has prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).
2. Minimize the prominence of the word '(b) (4)', by relocating it to follow the established name since it is distracting from other important information. For example: Revise the established name statement to read "Vasopressin Injection, USP) (b) (4)" on the same line.
3. Remove the words "USP Vasopressin" from the strength statement as it is redundant. Revise the strength statement to read "20 Units per mL".
4. Incorporate the package type "Multiple Dose Vial" on the label.
5. Add the statement "Must be diluted prior to use" on the principal display panel to inform the user that further dilution of this product is needed prior to intravenous administration.
6. Revise the abbreviation 'IV' to the word 'Intravenous' to help avoid the misinterpretation of 'IV' as the Roman numeral 4.

7. Revise the statement “ [REDACTED] (b) (4) [REDACTED] ” on the side panel to read “Discard diluted solutions after 18 hours at room temperature or 24 hours refrigerated.” In order to maintain consistency with information provided in the full prescribing information.

B. Carton Labeling

1. See comments 1-5 above.
2. Revise the statement on the side panel “ [REDACTED] (b) (4) [REDACTED] ” to “Discard diluted solutions after 18 hours at room temperature or 24 hours refrigerated to maintain consistency with information provided in the full prescribing information.
3. Remove the abbreviation “IV” from the statement “For Intravenous (IV) Infusion” on the principal display panel as it is duplicative and may be misinterpreted as the Roman numeral 4.
4. Revise the storage statement on the side panel to correspond with the storage condition statement in the insert labeling: “Store between 15°C and 25°C (59°F and 77°F)”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vasopressin that JHP Pharmaceuticals submitted on December 23, 2013.

Table 2. Relevant Product Information for Vasopressin	
Active Ingredient	Vasopressin, USP
Indication	To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) as an adjunct to fluids and catecholamines
Route of Administration	Intravenous
Dosage Form	Injection
Strength	20 USP Vasopressin Units per mL
Dose and Frequency	For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up at 10 to 15 intervals by 0.005 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasopressin by 0.005 units/minute every hour as tolerated to maintain target blood pressure.
How Supplied	1 mL vial (20 USP Vasopressin units per mL) in cartons of 25 multi-dose vials.
Storage	(b) (4) °C to 25°C ((b) (4) °F to 77°F)
Container Closure	The proposed container closure system consists of a 1 mL fill volume presentation. The 1 mL volume is supplied in a 3 mL (b) (4) clear glass vial, sealed with (b) (4) stoppers and (b) (4) seals. Each pack is comprised of 25 labeled vials in a carton.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 7, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date of search	January 17, 2013 (date of last search in OSE RCM# 2012-2808 dated June 7, 2013) to February 7, 2014
Drug Names	(Vasopressin or Vasopressin Tannate as active ingredient) (Pitressin as product name) (Pitressin as product verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

B.2 Results

No medication error cases were identified.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive (DMEPA's shared drive) on February 5, 2014 using the term, vasopressin, to identify reviews previously performed by DMEPA.

C.2 Results

- OSE RCM# 2012-2808 (b)(4) (vasopressin) Label and Labeling Review, completed June 7, 2013
- OSE RCM# 2012-2922 (b)(4) (vasopressin) Proprietary Name Review (unacceptable) completed March 6, 2013
- OSERCM# 2013-2679 Vasopressin (vasopressin) Proprietary Name Review (acceptable), completed February 5, 2014

APPENDIX D. HUMAN FACTORS STUDY- N/A

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on February 7, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	February 7, 2014 (no date restriction)
ISMP Newsletter Search Strategy	Select one of the following: Match Exact word or phrase Match Any of the words Match All of the words Boolean query
Search Terms	Vasopressin

E.2 Results

DMEPA searched ISMP publications on February 7, 2014 for additional medication error cases and actions concerning vasopressin. No relevant publications were identified.

APPENDIX F. REGULATORY HISTORY

F.1 Summary

The drug product Pitressin was previously manufactured and distributed by Parke-Davis since pre-1938 to 1940 for use in diabetes insipidus. We did not identify any records indicating that Pitressin was submitted for FDA approval during this time. At FDA request, NDA 19286 was later submitted by Parke Davis on May 9, 1984 for Pitressin (Vasopressin Injection, USP) for a labeling indication of use in the emergency management of acute upper gastrointestinal bleeding. However on December 13, 1984, Parke Davis requested withdrawal of application NDA 19286 without prejudice to a future filing. As far as we can tell, Parke Davis continued to market Pitressin without an approved NDA until the rights were sold to JHP Pharmaceuticals. Through a series of transactions, JHP acquired the manufacturing site, the trademark and all intellectual property associated with the drug product Pitressin, owned by Parke-Davis. On September 26, 2012, JHP submitted a 505(b)(2) NDA 204485 under "Type 7 - Drug Already Marketed without Approved NDA" for this product seeking the indication of vasodilatory shock (including post-cardiotomy shock and septic shock) based upon literature evidence.

On December 5, 2012, JHP submitted a request for proprietary name review for (b) (4). However, on March 6, 2013, the proposed proprietary name, (b) (4), was found unacceptable in OSE Review # 2012-2922 dated March 6, 2013 due to wrong drug medication errors seen with (b) (4), resulting in serious outcomes, including death.

JHP subsequently submitted revised labels and labeling to reflect their request for review of a different proprietary name, (b) (4) on May 17, 2013. The revised insert labeling also removed the warning against the dilution of this product in 5% dextrose in water (D5W) due to new compatibility data submitted by the Applicant that indicated (b) (4) is compatible with D5W. The proposed proprietary name, (b) (4) was withdrawn by the Applicant on June 24, 2013 subsequent to a June 12, 2013 teleconference.

JHP submitted revised labels and labeling reflecting their request for review of an alternate proprietary name, Vasostrict, on November 18, 2013. The proposed proprietary name, Vasostrict, was found unacceptable in OSE Review # 2013-2679 dated February 5, 2014.

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Vasostrict container label, carton labeling, and package insert labeling submitted by JHP Pharmaceuticals on November 18, 2013.

- Container label
- Carton labeling
- Full Prescribing Information (no image)

G.2 Label and Labeling Images

A. Container Label



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

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
02/12/2014

LISA V KHOSLA
02/14/2014

RHPM Overview – CR Action
NDA 204-485
Pitressin (vasopressin) Injection
20 USP vasopressin units per mL

Sponsor: JHP Pharmaceuticals, LLC
Classification: Standard
Letter Date: September 25, 2012
User Fee Receipt Date: September 26, 2012
User Fee Goal Date: July 26, 2013

Background

JHP Pharmaceuticals submitted this 505(b)(2) NDA for Pitressin (vasopressin injection, USP), Synthetic. Pitressin is a marketed, unapproved product, which, according to the applicant, has been available on the market for over 98 years for the treatment of diabetes insipidus. The applicant states that it is a pre-1938 drug and therefore categorized as a grandfathered product, manufactured and marketed by various companies without the approval of an NDA.

The proposed indication is for treatment of vasodilatory shock, including post-cardiotomy shock and septic shock. The applicant has submitted a literature-based NDA per discussion at the October 17, 2011 Pre-NDA Teleconference with DCRP (Pre-IND 112,944). (b) (4)

According to the applicant, Pitressin, formerly known as Pitressin Aqueous, currently marketed by JHP is the same product as the Pitressin drug product previously manufactured and distributed by Parke-Davis since pre-1938 for use in diabetes insipidus. Through a series of transactions, JHP has acquired the manufacturing site in Rochester, MI, the trademark, and all intellectual property (including know-how) associated with the Pitressin drug product, previously manufactured and marketed by Parke-Davis.

Two NDAs for Pitressin were previously submitted by Parke-Davis and reviewed in DMEP. NDA 3-402 for Pitressin Tannate in Oil Injection was approved in 1941 for diabetes insipidus. The product was subsequently withdrawn from marketing (NDA “withdrawn FR effective” on September 25, 1998) for reasons other than safety and efficacy. At the FDA’s request, Parke-Davis submitted NDA 19-286 for Pitressin (Vasopressin Injection, USP) on May 9, 1984 to add a labeling indication for use in the emergency management of acute upper gastrointestinal bleeding. However, Parke Davis subsequently requested withdrawal of NDA 19-286 on December 13, 1984. There have been no additional regulatory activities submitted for Pitressin until JHP Pharmaceuticals submitted this NDA 204-485 for the treatment of vasodilatory shock.

A CMC IR Letter was issued on 3-7-13. The applicant responded to the CMC IR Letter in an amendment dated 7-12-13 (received 7-15-13).

A LABELING PMR/PMC DISCUSSION COMMENTS Letter was issued on 6-26-13 with labeling comments and a request for a PREA PMR. The applicant responded to the LABELING PMR/PMC DISCUSSION COMMENTS Letter in an email dated 7-10-13 (official amendment dated and received 7-11-13). The amendment included a response only to the labeling comments.

Division Director's Memo

In his 7-18-13 review, Dr. Stockbridge wrote the following:

I conclude that enough information is available to support labeling to increase blood pressure, despite lack of long-term outcome data. Providing successful negotiations on the label, the sole basis for a complete response will be CMC issues. We will ask the sponsor if they can obtain data from the best of the few studies in children.

Cross-Discipline Team Leader (CDTL) Review

In her 6-13-13 review, Dr. Targum wrote the following:

- **Recommended Regulatory Action**

I recommend a Complete Response (non approval) action because of unresolved CMC deficiencies. Upon resolution of CMC issues, I would recommend approval of vasopressin for increasing mean arterial blood pressure in vasodilatory shock, including septic shock and post-cardiotomy vasodilatory shock (vasoplegic syndrome) for use in patients who remain hypotensive despite fluids and catecholamine administration.

The following primary reviews were completed (see DAARTS for the complete reviews and recommendations and conclusions):

Discipline	Reviewer	Completion Dates
Biopharmaceutics	Elsbeth Chikhale, Ph.D.	3-15-13
Product Microbiology	Erika Pfeiler, Ph.D.	4-5-13
Non-Clinical	Rama Dwivedi, Ph.D.	4-10-13
Quality	Lyudmila Soldatova, Ph.D.	5-8-13
Clinical Pharmacology	Peter Hinderling, M.D.	5-24-13; 5-28-13
Clinical	Monical Fiszman, M.D., Ph.D.	5-25-13
Biometrics	Fanhui Kong, Ph.D.	5-29-13

Environmental Assessment

The sponsor requested a Categorical Exclusion for environmental assessment (EA) pursuant to 21 CFR Part 25, which was found to be acceptable. See Quality review.

EER Report (Manufacturing Site Inspections)

The Office of Compliance issued an Overall Recommendation of "Acceptable" on 1-8-13; see Quality review.

Advisory Committee (AC) Meeting

Not applicable. It was determined that an AC Meeting was not needed.

Safety Update

See Dr. Fiszman's 5-25-13 Clinical Review.

Debarment Certification

A debarment certification was submitted on 9-26-12.

Financial Disclosure

Dr. Fiszman's 5-25-13 Clinical Review states: "There are no financial disclosures to review."

Office of Scientific Investigations (OSI)

During the 45-day Filing Meeting on 11-9-12, it was agreed that clinical site inspections were not applicable as this was a literature-based NDA.

In addition, Dr. Fiszman's 5-25-13 Clinical Review states the following:

3 Ethics and Good Clinical Practices

This was a literature-based application. The results of the published studies in this submission were collected long time ago and were conducted in several study sites located in different countries. For these reasons this reviewer had no access to raw data, cannot conduct site inspections, and cannot conclude about integrity of an individual trial. There are no financial disclosures to review.

Pediatrics

A PeRC meeting was held on 5-8-13. The PeRC disagreed with the Division's decision to grant the applicant's request for a full waiver. Instead, the PeRC recommended a postmarketing requirement (PMR) for the sponsor to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the Investigators of the published pediatric studies in this submission. See Dr. Targum's 6-13-13 CDTL review and Dr. Fiszman's 5-25-13 Clinical review for additional information.

Labeling

The original submission contains proposed draft labeling for the package insert (PI) in PLR format, and container and carton labeling. No Patient PI (PPI) was submitted.

PMHS provided comments on the proposed PI in a review dated 5-23-13.

OPDP provided comments on the proposed PI in a review dated 5-29-13.

DMEPA provided comments on the proposed container label, carton and PI in a review dated 6-7-13.

Labeling comments on the PI and carton and container were conveyed to the applicant in the LABELING PMR/PMC DISCUSSION COMMENTS Letter dated 6-26-13. The CMC IR Letter dated 3-7-13 also had contained labeling comments on the carton and container. The applicant submitted the revised PI and carton and container labeling in response to the 6-26-13 LABELING PMR/PMC DISCUSSION COMMENTS Letter in an amendment dated 7-11-13. The applicant also submitted revised carton and container labeling in a response to the 3-7-13 CMC IR Letter in an amendment dated 7-12-13. However, it was noted that the carton and container labeling versions dated 7-11-13 and 7-12-13 were different. In addition, the applicant had emailed on 7-10-13 the revised PI in response to the 6-26-13 LABELING PMR/PMC DISCUSSION COMMENTS Letter, but the emailed version was different than the version of the PI officially submitted to the NDA (amendment dated 7-11-13). A request for clarification regarding the discrepancies in the labeling versions was emailed to the applicant on 7-16-13 and 7-18-13.

Proprietary name review

DMEPA found the proposed name (b) (4) unacceptable on 3-6-13 (see DMEPA review in DAARTS). On 5-20-13, a request for proprietary name review was received for (b) (4) as the primary name with an alternate name of (b) (4). A teleconference between DMEPA and the applicant was held on 6-12-13 to discuss the proposed alternate names (see DMEPA 6-17-13 minutes of the teleconference). The alternate name (b) (4) was subsequently withdrawn on 6-24-13. To date, no new alternate name has been submitted.

OSE Consults

DPV-1 performed a search of the FDA Adverse Event Reporting System (AERS) for postmarket adverse event cases with a serious outcome for adult and pediatric patients with Pitressin (vasopressin) injection. See Dr. Mark Miller's review dated 1-22-13 in DAARTS.

Safety Discussion

Drs. Fiszman and Targum indicated at the Wrap-up/Safety Meeting on 6-20-13 that there were no safety concerns that would preclude approval of the application.

Postmarketing Requirements/Commitments (PMR/PMC)

A PREA PMR will be requested for the applicant “to attempt to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in [their] submission (e.g., Choong et. al. [2009]).” This PREA PMR was conveyed in the 6-26-13 LABELING PMR/PMC DISCUSSION COMMENTS Letter. To date, the applicant’s response to this PREA PMR request is pending.

User Fee

The sponsor paid the user fee in full (User Fee ID# PD3012638).

505(b)(2) Clearance

Per a 6-10-13 email from Miranda Raggio of the Regulatory Affairs Team/OND, this NDA is cleared for action from a 505(b)(2) perspective.

Safety Requirements Team (SRT) Clearance

The DRAFT CR Letter was cleared through the SRT on 7-18-13 per an email from Dave Kurtik of the SRT.

RPM Summary

In an internal meeting on 7-17-13, it was determined that there would not be enough time to review the CMC amendment dated 7-12-13 (received 7-15-13) before the PDUFA goal date of 7-26-13. Furthermore, the labeling responses dated 7-11-13 and 7-12-13 could not be reviewed due to the discrepancies in the different versions of the labeling submitted. To date, no response has been submitted regarding the PREA PMR. Therefore, a Complete Response (CR) Letter will be drafted for Dr. Stockbridge’s signature. The CR Letter will also include a Clinical Pharmacology IR comment.

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
7-19-13

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/s/

QUYNH M NGUYEN
07/19/2013

**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, Labeling and Packaging Review

Date: June 7, 2013

Reviewer: Kimberly DeFronzo, R.Ph, M.S., M.B.A.
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, Pharm.D, BCPS
Division of Medication Error Prevention and Analysis

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

Drug Name and Strength: Pitressin (Vasopressin Injection, USP)
20 USP Vasopressin units per mL

Application Type/Number: NDA 204485

Applicant/sponsor: JHP Pharmaceuticals

OSE RCM #: 2012-2808

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Pitressin (Vasopressin Injection, USP) 20 USP Vasopressin units per mL for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

The following regulatory history incorporates information from the February 1, 2013 submission by JHP Pharmaceuticals.

The drug product Pitressin was previously manufactured and distributed by Parke-Davis since pre-1938 for use in diabetes insipidus. Through a series of transactions, JHP acquired the manufacturing site, the trademark and all intellectual property associated with the drug product Pitressin, owned by Parke-Davis. Pitressin was used to treat diabetes insipidus until 1940 when a longer acting product, also manufactured by Parke-Davis, entered the market. This longer-acting Pitressin Tannate in Oil provided an alternative therapeutic mode and approach for the same indication. We did not identify any records indicating that the shorter acting Pitressin formulation was submitted for FDA approval during this time; however, the Pitressin in oil formulation was approved under NDA 003402 with the proprietary name Pitressin Tannate 5 pressor units/mL, and later withdrawn from sale for reasons other than safety or efficacy. At FDA request, NDA 19286 was later submitted by Parke Davis on May 9, 1984 for Pitressin (Vasopressin Injection, USP) for a labeling indication of use in the emergency management of acute upper gastrointestinal bleeding. However on December 13, 1984, Parke Davis requested withdrawal of application NDA 19286 without prejudice to a future filing. As far as we can tell, Parke Davis continued to market Pitressin without an approved NDA until the rights were sold to JHP. No additional regulatory activities were submitted for Pitressin until JHP Pharmaceuticals submitted NDA 204485 for the treatment of vasodilatory shock.

On September 26, 2012, JHP submitted a 505(b)(2) NDA 204485 under “Type 7 - Drug Already Marketed without Approved NDA” for this product seeking the indication of vasodilatory shock (including post-cardiotomy shock and septic shock) based upon literature evidence.

On December 5, 2012, JHP submitted a request for proprietary name review for (b) (4). No alternate name was submitted, and JHP cited (b) (4). However, on March 6, 2013, the proposed proprietary name, (b) (4), was found unacceptable in OSE Review # 2012-2922 dated March 6, 2013 due to wrong drug medication errors seen with (b) (4) resulting in serious outcomes, including death.

JHP subsequently submitted revised labels and labeling to reflect their new request for review of the proprietary name, (b) (4) on May 20, 2013. The revised insert labeling also removed the warning against the dilution of this product in 5% dextrose in water (D5W) due to new compatibility data submitted by the Applicant that indicated (b) (4) is compatible with D5W.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 20, 2013 submission.

- Active Ingredient: Vasopressin, USP (per ONDQA)
- Indication of Use: Vasodilatory shock including post-cardiotomy shock and septic shock
- Route of Administration: Intravenous
- Dosage Form: Solution for Infusion (per ONDQA)
- Strength: 20 USP Vasopressin Units per mL (per ONDQA)
- Dose and Frequency: For continuous IV infusion for the treatment of vasodilatory shock, (b) (4) should be diluted in a normal saline solution (0.9% sodium chloride) or 5% dextrose in water (D5W) to a concentration of 0.1 unit/mL to 1.0 unit/mL. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit.

Post-cardiotomy shock

Adults: For adult patients with catecholamine-refractory hypotension, a starting dose of 0.03 U/min to a maximum of 0.1 U/min should be used. Once hemodynamic stability (MAP of 60 mmHg – 70 mmHg) is achieved, catecholamine doses may be reduced incrementally in a stepwise fashion. Pre-existing conditions should be considered when determining the target MAP, and guided by the adequate maintenance of urine output, global perfusion, and blood lactate concentrations. When catecholamines are no longer required, the (b) (4) dose may be tapered by 0.005 U/min every hour, and discontinued when MAP has been stable for at least 8 hours.

Children: (b) (4) is not recommended in pediatric patients with post-cardiotomy vasodilatory shock.

Septic shock

Adults: (b) (4) should be started at 0.01U/min and increased to 0.03 U/min to maintain hemodynamic stability (target MAP 60 mmHg – 70 mmHg); a maximum dose of 0.067 U/min may be used. Pre-existing conditions should be considered when determining the target MAP, and guided by the adequate maintenance of urine output, global perfusion, and blood lactate concentrations. Catecholamine doses may be reduced incrementally in a stepwise fashion to maintain hemodynamic stability: target MAP of 60 mmHg – 70 mmHg. Once catecholamines are no longer required, the (b) (4) dose may be tapered by 0.005 U/min every hour, and discontinued when MAP has been stable for at least 8 hours.

Children: (b) (4) is not recommended for use in pediatric patients with septic shock.

Once catecholamines are no longer required to maintain target MAP (60 mm Hg – 70 mm Hg), the (b) (4) dose may be tapered by 0.005 U/min every hour, and discontinued when MAP has been stable for at least 8 hours.

- How Supplied: (b) (4) (Vasopressin Injection, USP) (b) (4) is supplied as 1 mL vial (20 USP Vasopressin units per mL) in packages of 25 vials (NDC 42023-164-25).
- Storage: Store between (b) (4)°C and 25°C ((b) (4)°F and 77°F). See USP Controlled Room Temperature.
- Container and Closure Systems: The proposed container closure system consists of a 1 mL fill volume presentation. The 1 mL volume is supplied in a 3 mL (b) (4) (b) (4) USP Type I (b) (4) clear glass vial, (b) (4) (b) (4) stoppers and (b) (4) seals. Each pack is comprised of 25 labeled vials in a carton.

2 METHODS AND MATERIALS REVIEWED

We searched the FDA Adverse Event Reporting System (FAERS) database and reviewed the Pitressin label, carton, and package insert labeling submitted by the Applicant. Refer to Appendix A for a description of the FAERS database.

2.1 SELECTION OF MEDICATION ERROR CASES

FAERS Database Search

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date of search	January 17, 2013 (without date limit)
Drug Names	(Vasopressin or Vasopressin Tannate as active ingredient) (Pitressin as product name) (Pitressin as product verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS search retrieved 39 cases. Each case was reviewed for relevancy and duplication. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 17 cases were excluded from further analysis for the reasons stated below:

- Adverse events unrelated to medication error (n=3)
- Use of recalled product (n=1)

- Product Quality Issue unrelated to medication error (n=1)
- Medication error where Pitressin was a concomitant medication only (n=8)
- Wrong technique error involving improper mixing of Vasopressin Tannate in Oil formulation which was withdrawn from the market (n=1)
- Duplicate cases (n=3)

2.2 LITERATURE SEARCH

DMEPA searched PubMed and the ISMP publications on February 14, 2013 for additional medication error cases and actions concerning Pitressin or vasopressin. No relevant publications were identified.

2.3 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Proposed Container Label submitted May 20, 2013 (Appendix B)
- Proposed Carton Labeling submitted May 20, 2013 (Appendix C)
- Proposed Insert Labeling submitted May 20, 2013 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

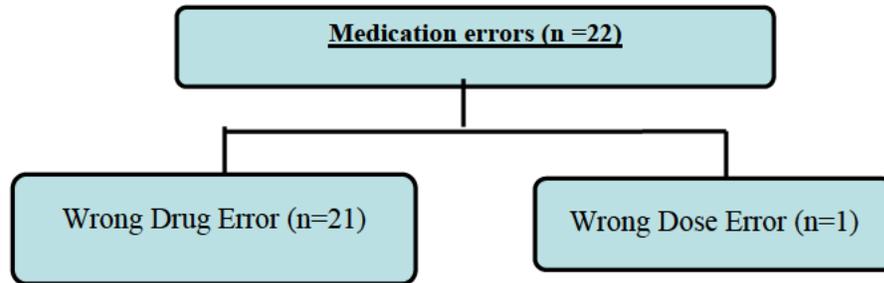
The following sections describe the results of our FAERS search and the risk assessment of the Pitressin product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, sixteen Pitressin medication error cases remained for our detailed analysis. Duplicates were merged into a single case. 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 reporter¹. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all case numbers for the cases summarized in this review.

¹ 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

Figure 1: Pitressin medication error cases categorized by type of error (n = 22)



Wrong Dose Error

We identified one case of “wrong dose” received June 20, 2001. This case involved a female child (age unknown) who received Pitressin (dose unknown) for unknown treatment. The case reported that the patient was “improperly dosed” and subsequently died. No additional information was provided in the narrative.

Wrong Drug Errors

We identified 21 wrong drug errors where similarities in the labels (i.e. similar colors used on labels) and/or container closures (i.e. same size vials or same color caps) were cited as contributing factors in 16 of the 21 cases. These cases involved confusion between Pitressin or Vasopressin with Dilantin, Phenytoin, Adrenalin, Atropine, Hydralazine, and Zofran from varying manufacturers.

The remaining 5 wrong drug errors were due to (b) (4) occurring with the product (b) (4). The narratives in these cases cited confusion occurred between the names (b) (4) which led to the use of the wrong product and caused harm in the patient. A detailed discussion of these cases can be found under the separate name review for (b) (4) (OSE RCM# 2012-2922 dated March 6, 2013).

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Our review of the medication errors retrieved from the FAERS database identified one wrong dose error and 21 wrong drug errors. A labeling meeting was held on May 14, 2013, where dosing information regarding up titration and discontinuation of vasopressin was added, and we find this information adequate. However, our review of the proposed insert labeling identified areas that can be improved to minimize confusion that can lead to dosing errors (see Section 4 for our recommendations). Additionally, per consultation with the Office of New Drug Quality Assessment (ONDQA), it was confirmed that the use of the word (b) (4) throughout the insert labeling is not a requirement and should be removed.

In our evaluation of the wrong drug errors, we note that these wrong drug errors were attributed to either name confusion and/or labeling confusion. As discussed in OSE review 2012-2922, some wrong drug errors were due to orthographic and phonetic similarities between the products (b) (4). Consequently, the request for the

(b) (4) of the name (b) (4) was denied by DMEPA in attempts to mitigate further name confusion between these two names.

The wrong drug errors that were attributed to label and labeling confusion between Pitressin or Vasopressin with other injectable products on the market are difficult to mitigate since there are many vial sizes and cap colors for the various products cited in the cases. Therefore, requesting the Applicant or other drug manufacturers to relabel or repackage their respective product(s) may create a different look-alike situation with another drug on the market that did not previously exist. Our main solution for minimizing wrong drug errors is to ensure clear labels and labeling for our product with easily identifiable important information such as the drug name and strength.

Historically, vasopressin has been used via intramuscular, subcutaneous, and intravenous routes of administration. However, for the proposed indication of vasodilatory shock (including post-cardiotomy shock or septic shock), vasopressin should only be administered as an intravenous infusion. Due to the previous use of other routes of administration by healthcare practitioners, the intended intravenous route of administration should be clearly noted on the principal display panel of the container label and carton labeling to minimize the risk of wrong route of administration errors.

The proposed dosing for continuous intravenous infusion of (b) (4) (vasopressin) ranges from 0.01 units/min to 0.1 units/min, which requires the compounding of a diluted intravenous vasopressin solution. We note that the currently proposed dosage and administration section of the insert labeling does not provide any directions on how to prepare a dilute intravenous vasopressin solution for continuous infusion. This information should be provided in the insert labeling to assist the user on how to accurately dilute this product and avoid potential calculation errors that may occur during the use of this product. The proposed insert labeling recommends that (b) (4) be diluted in a normal saline solution to a concentration of 0.1 unit/mL or 1 unit/mL. Due to the numerical similarity in these dilution concentrations, we recommend providing two distinct sets of directions, one for each concentration, to avoid confusion

To determine the proper amount of diluent required for dilution, we need to consider the variability in dosing and the need for customized dose adjustments to titrate to the desired blood pressure. With a solution concentration of 0.1 unit/mL, at a dosing range of 0.01 units/min to 0.1 units/min, a patient would receive anywhere from 6 mL/hour to 60 mL/hour. With a solution concentration of 1 unit/mL, at a dosing range of 0.01 units/min to 0.1 units/min, a patient would receive anywhere from 0.6 mL/hour to 6 mL/hour. Per the Office of New Drug Quality Assessment (ONDQA), once vasopressin is diluted for infusion, there is data to support 18-hour sterility and 48 hour stability only. Therefore, a single bag should not be used beyond 18-hours at room temperature. A patient receiving a solution concentration of 0.1 unit/mL could receive anywhere from 108 mL to 1080 mL in an 18-hour period. A patient receiving a solution concentration 1 unit/mL could receive anywhere from 10.8 mL to 108 mL in an 18-hour period. Given this range in volume that a patient can receive in an 18 hour period, the dilution instructions will need to provide for a practical final volume that is appropriate for the sterility and stability of the product and minimizes the risk for inadvertent use of a diluted solution beyond 18 hours.

Considering the totality of this information, we recommend that instructions for creating a solution concentration of 0.1 unit/mL use a 500 mL bag of a compatible diluent since this is a standard volume stocked in most hospitals and can be doubled for patients receiving the maximum dose. Alternatively, for patients that require fluid-restriction, the recommended higher concentration of 1 unit/mL may be more appropriate and can be compounded using a bag size of 100 mL of a compatible diluent since this is also a standard volume stocked in most hospitals. While the use of a bag size of 50 mL would also be appropriate given the ten-fold difference in concentration, we avoid the use of the 50 mL bag size due to its numerical similarity to the 500 mL bag size which may lead to compounding errors should the zero is overlooked by the preparer.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to approval of this NDA:

Insert Labeling:

1. On June 14, 2006, the Agency, in conjunction with ISMP, launched a campaign to warn healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations such as trailing zeros, or symbols. As part of this campaign, FDA agreed not to use such error prone designations in their approved product labeling because they are carried onto the prescribing practice. The abbreviations “IV, U” and trailing zero can be found in the Dosage and Administration section of insert labeling for this product. We recommend replacing the abbreviation such as ‘U’ with the appropriate full meaning of ‘unit’ or the abbreviation such as ‘IV’ with the appropriate full meaning of ‘intravenous’. In addition, trailing zeros is also error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. ‘1.0’ can be misinterpreted as ‘10’); thus, we recommend removing the trailing zeros where they appear in the insert labeling.
2. Add the appropriate unit of measure to follow each corresponding number throughout the insert labeling (e.g., the temperature designations of °C or °F for the storage conditions in Section 16 or unit/mL or units/minute in Section 2).
3. To improve clarity of the “in-use” stability of the vial after puncture, we recommend replacing the current statement “(b) (4)” with language that will be more readily understood by clinicians such as “Discard vial 28 days after first puncture” in section 16 “How Supplied/Storage and Handling” of the insert labeling.
4. The Dosage and Administration section instructs the user to dilute the product in a normal saline solution to a concentration of “0.1 to 1 unit/mL”. However, no additional guidance is provided to aid practitioners in preparing the desired

dilution. Therefore, we recommend incorporating dilution instructions in a table format in a separate section within Section 2, *Dosage and Administration*, that follows the dosing recommendations similar to the following example:

2.1 PREPARATION OF DILUTED SOLUTIONS

Pitressin should be diluted in a compatible diluent prior to use. Discard unused diluted solution after 18 hours.

For Patients Without Fluid Restriction: Dilute “Tradename” to a concentration of 0.1 unit/mL as follows (in Table 1):

Table 1: Instructions to Prepare 0.1 USP units/mL Dilution

Final Concentration	USP units of Pitressin (20 USP units/mL) vial	Volume of Diluent
0.1 USP unit/mL	50 USP units (2.5 mL of 20 USP units/mL)	500 mL

For Fluid-Restricted Patients: Dilute “Tradename” to a concentration of 1 unit/mL as follows (in Table 2):

Table 2: Instructions to Prepare 1 USP unit/mL Dilution

Final Concentration	USP units of Pitressin (20 USP units/mL) vial	Volume of Diluent
1 USP unit/mL	100 USP units (5 mL of 20 USP units/mL)	100 mL

4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA.

A. Container Labels

1. Ensure the established name “Vasopressin Injection, USP” is printed in letters that are at least ½ the size of letters comprising the proprietary name, and the established name has prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).
2. Update the strength presentation to ensure the abbreviation ‘USP’ is presented in ½ the size of the number ‘20’ to help prevent the letter ‘U’ from being misinterpreted as the number ‘0’. For example: ‘20 USP units per mL’.
3. Minimize the prominence of the word “(b) (4)” by relocating it to follow the established name since it is distracting from other important information. For example: Revise the established name statement to read “Vasopressin Injection, USP) (b) (4)” on the same line.
4. Remove the word “Vasopressin” from the strength statement as it is redundant.
5. Incorporate the package type “Multiple Dose Vial” on the label.
6. On June 14, 2006, the Agency, in conjunction with ISMP, launched a campaign to warn healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations such as trailing zeros, or symbols. As part of this campaign, FDA agreed not to use such error prone designations in their approved product labeling because they are carried onto the prescribing practice. Accordingly, if space permits, the abbreviation ‘IV’ should be replaced with the word ‘intravenous’ to help avoid the misinterpretation of ‘IV’ as the Roman numeral 4.
7. Remove the statements “(b) (4)” from the side panel as this information is more appropriate to include in the Dosage and Administration section of the insert labeling.

B. Carton Labeling

1. See comments 1-5 above.
2. Remove the statement “(b) (4),” from the side panel as this information is more appropriate to include in the Dosage and Administration section of the insert labeling.

3. Remove the abbreviation “IV” from the statement “For Intravenous (IV) Infusion” on the principal display panel as it is duplicative and may be misinterpreted as the Roman numeral 4.
4. Add the warning statement ‘Must be diluted before infusion’ (or similar language) as a reminder for the user that this product must be diluted prior to use.
5. Add the appropriate unit of measure (°C or °F) to the temperature in the storage condition statement for clarity of this information and to match the information found in the insert labeling under ‘Storage’ section.

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

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data 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 reports for every adverse event or medication error that occurs 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, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

Appendix D: Case numbers for the medication error cases identified in FAERS

Case #
4031198
7387647
8848916
6640368
7077039
7261054
7498141
7555212
8280636
8291986
8636993
8848939
8877139
8877145
3676856
6999005
8737337
3991532
5793862
5105972
5105976
3411972
3696143
3732185
5284531
5700026
5760034
6571235
3979997
3988399
5791120
5745434
7631505
8447938
7118496
5791006
5766898
5792870
5117535

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/s/

KIMBERLY A DE FRONZO
06/07/2013

IRENE Z CHAN
06/07/2013

SCOTT M DALLAS
06/07/2013

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

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

Memorandum

Date: May 29, 2013

To: Quynh Nguyen
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Emily Baker
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: (b) (4) (vasopressin) Injection
NDA: 204485
Comments on draft product labeling

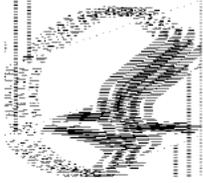
OPDP has reviewed the proposed Package Insert (PI) submitted for consult on December 4, 2012, for (b) (4) (vasopressin) Injection. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI. Our comments are based on the proposed labeling emailed to us on May 21, 2013.

Thank you for the opportunity to comment on the proposed PI. If you have any questions on the comments for the PI, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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/s/

EMILY K BAKER
05/29/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: May 23, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Pitressin[®] (vasopressin, injection, USP)

NDA: 204-485

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Applicant: JHP Pharmaceuticals, LLC.

Materials Reviewed: Pitressin labeling, submitted February 1, 2013.

Consult Question: “Please review and provide edits to the proposed Content of Labeling for the following section: 8.3 PREGNANCY.”

INTRODUCTION

On September 25, 2012, JHP Pharmaceuticals, LLC., submitted a 505(b)(2) New Drug Application for Pitressin (vasopressin) Injection, a marketed unapproved drug, for the proposed indication of vasodilatory shock (including post-cardiotomy shock and septic shock). In a Pre-IND (PIND 112,944) meeting between the sponsor and the Division of Cardiovascular and Renal Products (DCRP) on October 17, 2011, the DCRP agreed that it was acceptable for the sponsor to provide a literature-based review for the proposed indication given the extensive clinical experience with the product over several decades.

The Division of Cardiovascular and Renal Products (DCRP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Pitressin labeling.

This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Pitressin (vasopressin, injection, USP) is a synthetic version of vasopressin identical to the natural peptide produced in the posterior pituitary gland. Pitressin is available as an intravenous solution at a concentration of 20 pressor units/mL, and contains the preservative chlorobutanol (a chloroform derivative). This product (manufactured by JHP Pharmaceuticals) is the same product originally marketed by Parke-Davis. Pitressin is a pre-1938 drug product that has never received FDA approval, but has been marketed for almost 100 years. In June 2006, FDA announced a new drug safety initiative to remove unapproved drugs from the market, and issued a final guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide (CPG)," outlining its enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process. This application, NDA 204-485, is the first Pitressin product seeking FDA approval.

The natural peptide vasopressin, also known as antidiuretic hormone, is stored in the posterior pituitary in mammals and secreted by the hypothalamus. Its primary role in the body is to regulate serum osmolality and vascular tone.¹ Vasopressin stimulates the renal vasopressin V2 receptors which are coupled to adenylyl cyclase and cyclic AMP which causes increased water permeability at the luminal surface of the distal convoluted tubule and collecting duct, leading to increased free water reabsorption and resulting in increased urine osmolality and decreased urinary flow. In addition, vasopressin directly stimulates contraction of smooth muscle V1 receptors which mediates its vasoconstrictive effects.¹

Role of naturally occurring vasopressin in pregnancy

Systemic arterial vasodilation occurs early in the first trimester prior to the maturation of the placenta.² Arterial vasodilation early in pregnancy is believed to be associated with a decline in plasma osmolality and an increase in thirst and increase in water intake stimulating the release of

¹ McEvoy, Gerald, et al. "Vasopressin." *AHFS Drug Information*. 2012. *Stat!Ref*. Web. 1 May 2013.

² Schrier, Robert W. *J Am Soc Nephrol*. Systemic Arterial Vasodilation, Vasopressin and Vasopressinase in Pregnancy. 21:570-572, 2010

vasopressin. Vasopressinase, a cystine aminopeptidase produced by the trophoblasts of the placenta enhances the clearance of vasopressin. Vasopressinase levels increase four-fold during the middle and late stages of pregnancy, thus increasing the clearance of vasopressin. vasopressin levels return to normal approximately 3 months postpartum.²

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Studies have not been conducted with Pitressin in pregnant woman or in animals; hence, the pregnancy category C designation (see 22 CFR 201.57(c)(9)(i)(3)). Clinical Pharmacology updated the Dosing and Administration and the Clinical Pharmacology sections of Pitressin labeling with dosing and pharmacokinetic information from a review of published literature. Appropriate cross-references were placed in the pregnancy subsection of Pitressin labeling.

The Drugs and Lactation Database (LactMed)³ was searched for available lactation data on with the use of Pitressin or vasopressin, and no information was located. Hale (2006)⁴ reported that although vasopressin is probably present in human milk, it is rapidly destroyed in the gastrointestinal tract, and systemic absorption through breast milk feeding is unlikely. Alternatively, a lactating woman may choose to pump and discard breast milk for 5 half-lives after administration of Pitressin (approximately 1.5 hours) in order to avoid any exposure to an infant through breast milk. Drugs, with the exception of radiopharmaceuticals, are considered eliminated from the systemic circulation between 4 to 5 half-lives.

CONCLUSION

The pregnancy subsection of Pitressin labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of Pitressin labeling was revised to comply with current labeling recommendations.

³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

⁴ Hale, T. Medications and Mothers Milk, 12th ed. Hale Publishing, 2006

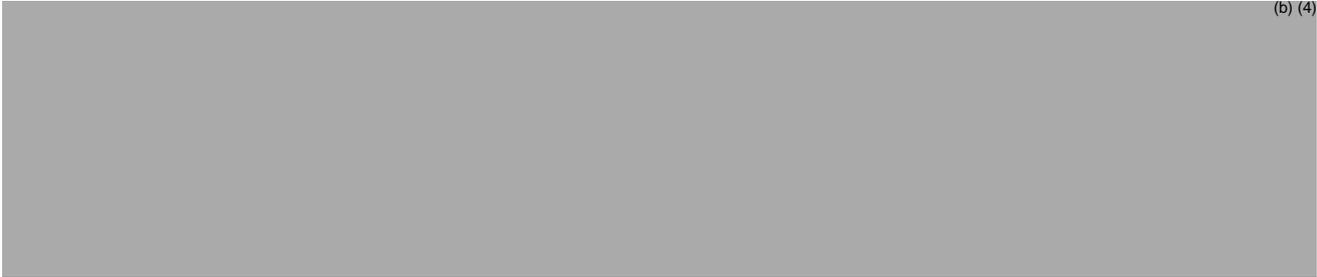
The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on May 9, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----**USE IN SPECIFIC POPULATIONS**-----



(b) (4)

Reviewer comment: As noted in the Label Review Tool from SEALD, pregnancy category should not be in the highlights of prescribing information section. In addition, clinical pharmacology will update Dosing and Administration under Highlights.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C



(b) (4)

Risk Summary

There are no adequate or well-controlled studies of (b) (4) in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin.

Clinical Considerations

(b) (4) vasopressin (b) (4) may produce tonic uterine contractions that could threaten the continuation a pregnancy (b) (4)

Reviewer comment: Labeling subsections 8.1 through 8.5 are specified by regulation (see 201.57(c)(9)). These subsections may not be re-numbered or have headings altered.

Reviewer comment: PMHS-MHT recommends deleting subsection 8.2 as there is no known information on the effects of Pitressin on labor and delivery.

8.3 Nursing Mothers

It is not known whether (b) (4) is present in human milk. However, oral absorption of (b) (4) by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. A lactating woman may choose to pump and discard breast milk for 1.5 hours after receiving (b) (4) to minimize potential exposure to the breastfed infant. Caution should be exercised when (b) (4) is administered to a nursing woman

17 PATIENT COUNSELING INFORMATION

This section did not receive any edits from PMHS-MHT as this product is only used under the supervision of a physician.

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/s/

CARRIE M CERESA
05/23/2013

JEANINE A BEST
05/23/2013

LYNNE P YAO
05/24/2013

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

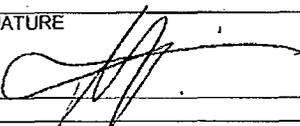
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Gerald Vasquez	TITLE Manager, Regulatory Affairs
FIRM/ORGANIZATION JHP Pharmaceuticals LLC	
SIGNATURE 	DATE (mm/dd/yyyy) 03/06/2013

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850



March 6, 2013

Attachment to Form FDA 3454

21 CFR 54: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

54.4 - Certification and disclosure requirements.

JHP's NDA 204485 for Pitressin® Injection (vasopressin injection) is based on a review of the clinical data available in the literature. JHP did not sponsor any clinical studies or have any financial arrangement with the authors of the clinical studies cited in the NDA 204485. A list of the authors and references cited in the clinical sections of the NDA is provided on the following pages (from NDA 204485, Module 2.5 References).

JHP hereby certifies that there were no clinical investigators who are full-time or part-time employees of JHP. JHP also certifies that there was no contact with the authors while they were conducting the studies or writing the publications.

During the preparation of the NDA, JHP consulted with Dr Cheryl Holmes as a Key Opinion Leader in the field of Septic Shock. Dr. Holmes' contact information is listed below. JHP certifies that studies cited in the NDA where Dr. Holmes was an author were completed well before JHP began preparation of the NDA and there was no financial incentive between JHP and Dr. Holmes with respect to the outcome of the studies.

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**Gerald
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Gerald Vasquez, Manager of Regulatory Affairs

**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: January 22, 2013

Reviewer(s): Mark S. Miller, PharmD
Division of Pharmacovigilance I (DPV-I)

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

Product Name(s): Pitressin (Vasopressin) Injection

Subject: All Adverse Events with Serious Outcome(s)

Application Type/Number: NDA 204-485

Applicant/Sponsor: JHP Pharmaceuticals LLC

OSE RCM #: 2012-2876

1 INTRODUCTION

The Division of Cardiovascular and Renal Products (DCRP) requested a search of the FDA Adverse Event Reporting System (FAERS) for postmarket adverse event cases with a serious outcome for adult and pediatric patients with Pitressin (vasopressin) injection. This information was requested to help support an NDA review. The proposed indication for Pitressin (vasopressin injection) is vasodilatory shock including post-cardiotomy shock and septic shock. Pitressin® (vasopressin injection) is a drug product that has been commercially available for over 100 years (pre-1938 drug), with a formulation that contains amounts of the active ingredient vasopressin and the excipient (preservative) chlorobutanol.

2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy	
Date of search	January 2, 2013
Time period of search	January 1, 1968 to January 2, 2013
Product Terms	Vasopressin, Vasopressin Tannate, Pitressin
MedDRA Search Terms	All adverse events
Additional criteria	<i>Serious</i> outcome
Age criteria	Search 1: 18 years of age or older (adult patients) Search 2: 17 years of age or younger (pediatric patients)

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

Table 2. Data Mining Search Strategy	
Data Refresh Date	August 27, 2012
Product Terms	Vasopressin
Empirica Signal Run Name	Generic by Age, Suspect Drugs only
MedDRA Search Strategy	All Adverse Events

See Appendix for a description and limitations of the FAERS and Empirica databases.

3 DATA

FDA Adverse Event Reporting System (FAERS)

An assessment of a causal relationship between the adverse events and vasopressin was not completed by the reviewer. Using the search strategy in Table 1, FAERS retrieved 88 adult cases and 16 pediatric cases with vasopressin use (See Table 3). See below FAERS Crude Counts of All Preferred Terms in Cases in Table 4 and Table 5 and a Line Listing of Case Characteristics in Table 6 and Table 7 which may contain duplicate cases.

Table 3. Total number of FAERS reports for vasopressin with a serious outcome*

All events from January 1, 1968 to January 2, 2013

	Serious [‡] (US)	Death (US)
Adults (≥18 years)	88 (46)	33 (10)
Pediatrics (0-17 years)	16 (5)	7 (2)
Total	104 (51)	40 (12)

* May include duplicates and have not been assessed for causality

^ US counts in parentheses

‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Table 4. Most Frequently Reported MedDRA PTs with N≥2 for Vasopressin in pediatric cases with serious outcome received by FDA as of January 2, 2013.

Preferred Term	Count of Events	Percent of Total Cases
Rhabdomyolysis	4	25%
Acidosis	2	12.50%
Bacteraemia	2	12.50%
Hyperkalaemia	2	12.50%
Platelet count decreased	2	12.50%
Renal failure acute	2	12.50%
Bradycardia	2	12.50%
Necrotising fasciitis	2	12.50%
Pulmonary embolism	2	12.50%
Pulmonary hypertension	2	12.50%
Right ventricular hypertrophy	2	12.50%
Tricuspid valve incompetence	2	12.50%

% of Total: The total number of cases may not sum because a case may contain more than one event term.

The percent count of cases for each term is based on the count of PTs divided by the total count of cases

Table 5. Most Frequently Reported MedDRA PTs with N≥4 for Vasopressin in adult cases with serious outcome received by FDA as of January 2, 2013.

Preferred Term	Count of Events	Percent of Total Cases
Hypotension	14	15.91%
Rhabdomyolysis	12	13.64%
Cardiac arrest	9	10.23%
Bradycardia	7	7.95%
Myopathy	7	7.95%
Renal failure acute	7	7.95%
Blood creatine phosphokinase increased	6	6.82%
Diabetes insipidus	6	6.82%
Pulmonary oedema	6	6.82%
Drug ineffective	6	6.82%
Death	5	5.68%
Hypernatraemia	5	5.68%
Hyponatraemia	5	5.68%
Pulse absent	5	5.68%

Table 5. Most Frequently Reported MedDRA PTs with N≥4 for Vasopressin in adult cases with serious outcome received by FDA as of January 2, 2013.

Preferred Term	Count of Events	Percent of Total Cases
Blood pressure decreased	4	4.55%
Drug interaction	4	4.55%
General physical health deterioration	4	4.55%
Optic ischaemic neuropathy	4	4.55%
Pneumonia	4	4.55%
Respiratory failure	4	4.55%
Toxicity to various agents	4	4.55%

% of Total: The total number of cases may not sum because a case may contain more than one event term. The percent count of cases for each term is based on the count of PTs divided by the total count of cases

Data Mining of FAERS using Empirica Signal

Graph 1 below illustrates data mining safety signals with Vasopressin within various age groups. The rows list the Preferred Terms (PTs) or single medical concepts and the columns list the age ranges. The numbers in the tiles indicate the number of adverse event reports and the colors indicate the various EB05 scores. The darker the tiles, the higher the EB05 score. An additional restriction for this graph is EB05 scores of at least greater than 2. Typically, EB05 scores greater than 2 indicate a potential safety signal. No cases (no safety signals) were identified in patients ≤ 16 years of age.

Graph 1: 2012 Data Mining results for Vasopressin

Listing Preferred Terms (PTs) with EB05 scores >2

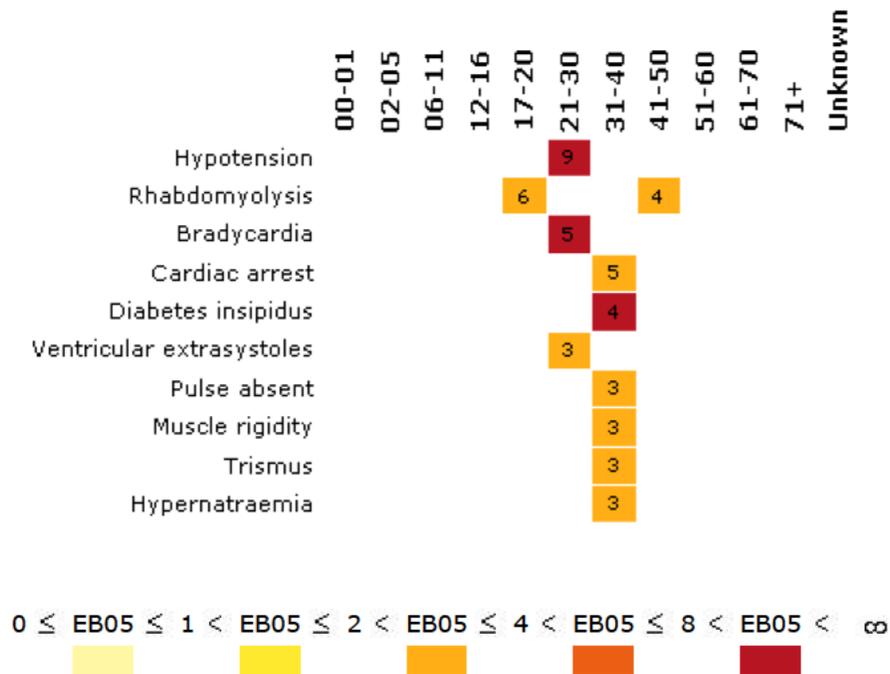


Table 6. Case Characteristics for pediatric patients with Vasopressin (N=16)									
	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
1	8202532	2	GB-PFIZER INC-2011254792	11/3/2011	17	U	GBR	RHABDOMYOLYSIS	Hospitalized, Other Serious
2	8226356	1	GB-WATSON-2011-18012	11/3/2011	17	U	GBR	BACTERAEemia;RHABDOMYOLYSIS	Other Serious
3	8215720	1	GB-NAPPMUNDI-GBR-2011-0008937	10/31/2011	17	U	GBR	RENAL FAILURE ACUTE	Hospitalized
4	8209017	1	PHHY2011G B92948	10/28/2011	17	U	GBR	HYPOPHOSPHATAEMIA;RENAL FAILURE ACUTE;ACIDOSIS;HYPERKALAEMIA;RHABDOMYOLYSIS;BACT ERAEMIA;STAPHYLOCOCCAL SEPSIS	Other Serious
5	7385902	1	20100177	5/5/2010	2	F	JPN	INTERNATIONAL NORMALISED RATIO INCREASED;MELAENA;PLATELET COUNT DECREASED	Other Serious
6	7246905	3	GB-SANOFI-AVENTIS-2009SA011828	3/16/2010	16	F	GBR	PULMONARY HYPERTENSION;RIGHT VENTRICULAR HYPERTROPHY;TRICUSPID VALVE INCOMPETENCE;PULMONARY EMBOLISM	Death, Hospitalized
7	7225454	3	GB-PFIZER INC-2009310835	2/19/2010	16	F	GBR	PULMONARY EMBOLISM;TRICUSPID VALVE INCOMPETENCE;PULMONARY HYPERTENSION;RIGHT VENTRICULAR HYPERTROPHY	Death, Hospitalized, Other Serious
8	6377835	1	070419-0000415	5/1/2007	infant	M	JPN	DISSEMINATED INTRAVASCULAR COAGULATION;PATENT DUCTUS ARTERIOSUS;STAPHYLOCOCCAL INFECTION;HYPERKALAEMIA;ARRHYTHMIA NEONATAL;ELECTROCARDIOGRAM QRS COMPLEX PROLONGED;NEONATAL CARDIAC FAILURE;NECROTISING FASCIITIS;NEUTROPHIL COUNT DECREASED;PLATELET COUNT DECREASED;NEONATAL DISORDER;NO THERAPEUTIC RESPONSE;NEONATAL INFECTION;SHOCK;CEREBRAL HAEMORRHAGE NEONATAL;BLOOD PRESSURE DECREASED;BRADYCARDIA NEONATAL	Death
9	6283378	2	JP-MERCK-0703USA04511	4/20/2007	infant	M	JPN	NECROTISING FASCIITIS	Death
10	4127069	1	JP-MERCK-0402USA01602	4/19/2004	16	M	JPN	HEPATIC FUNCTION ABNORMAL;Amylase increased;LIPASE INCREASED;ASPARTATE AMINOTRANSFERASE INCREASED;ALANINE AMINOTRANSFERASE INCREASED;Arteriovenous fistula	Other Serious

	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
11	5285945	1	0810106950001	8/30/1995	14	F	JPN	HYPOKALAEMIA;BRADYCARDIA;CARDIAC FAILURE;RHABDOMYOLYSIS	Death
12	5115355	1	28882	4/29/1994	17	F	USA	APNOEA;CONVULSION;HYPERSENSITIVITY;PALLOR	Hospitalized,Life Threatening
13	5110478	1	29620	4/25/1994	17	M	USA	ACIDOSIS;BLOOD CREATINE PHOSPHOKINASE INCREASED;HYPOCALCAEMIA;MYOPATHY	Death
14	5053152	1		11/3/1993	infant	M	USA	HYPOTENSION;ARRHYTHMIA;BRADYCARDIA	Life Threatening
15	4707207	1	904200001	3/19/1990	16	F	USA	ENCEPHALOPATHY;HYPONATRAEMIA	Hospitalized
16	4364647	1	00080008	3/30/1981	15	M	USA	DRUG INEFFECTIVE	Death

U=Unknown; Country Codes: JPN=Japan; GBR=United Kingdom; USA=United States of America

	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
1	7915465	2	DE-GENZYME-CAMP-1001409	7/10/2012	62	M	AUT	SKIN LESION;FEBRILE NEUTROPENIA;PSEUDOMONAL SEPSIS;SEPTIC SHOCK;TACHYCARDIA;CANDIDA PNEUMONIA;BRONCHOPNEUMONIA;ATRIAL FIBRILLATION;RESPIRATORY DISTRESS;TRACHEITIS;GENERAL PHYSICAL HEALTH DETERIORATION;LACTIC ACIDOSIS;RESPIRATORY FAILURE	Death,Hospitalized
2	8636993	1	GB-ROXANE LABORATORIE S, INC.-2012-RO-01432RO	6/26/2012	50	F	GBR	MULTIPLE DRUG OVERDOSE;PULMONARY OEDEMA;VOMITING;RENAL IMPAIRMENT;HYPERKALAEMIA;HYPOTENSION;METABOLIC ACIDOSIS;ANURIA;HYPOXIA	Hospitalized
3	8539184	2	JP-JHP PHARMACEUTICALS, LLC-JHP201200231	6/22/2012	79	M	JPN	DRUG INEFFECTIVE FOR UNAPPROVED INDICATION	Other Serious
4	8447938	1	20120095	3/1/2012	28	F	USA	WRONG DRUG ADMINISTERED;PROCEDURAL COMPLICATION;PULSE ABSENT;BLOOD PRESSURE IMMEASURABLE;ACCIDENTAL EXPOSURE;VASOSPASM;HYPOTENSION	Other Serious
5	8391276	1	2012MA000545	1/23/2012	55	M	USA	THROMBOCYTOPENIA;TREATMENT NONCOMPLIANCE;HYPOTENSION;PNEUMONIA;ISCHAEMIC HEPATITIS;RENAL FAILURE ACUTE	Hospitalized,Life Threatening,Other Serious

Table 7. Case Characteristics for adult patients with Vasopressin (N=88)									
Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome	
6	8343612	1	US-JHP PHARMACEUTICALS, LLC-JHP201200016	1/19/2012	32	M	USA	DIABETES INSIPIDUS;WITHDRAWAL SYNDROME	Other Serious
7	8334518	1	GB-JHP PHARMACEUTICALS, LLC-JHP201200002	1/12/2012	75	M	GBR	DIABETES INSIPIDUS;DRUG WITHDRAWAL SYNDROME	Other Serious
8	8264150	3	US-ASTELLAS-2011US007859	12/15/2011	37	M	USA	CARDIOMYOPATHY;DEATH	Death,Other Serious
9	8280636	1	IN-ROXANE LABORATORIES, INC.-2011-RO-01741RO	12/8/2011	28	F		METABOLIC ACIDOSIS;NON-CARDIOGENIC PULMONARY OEDEMA;RENAL FAILURE ACUTE;SHOCK;HYPOTENSION;HYPERKALAEMIA;INTENTIONAL OVERDOSE;ACUTE RESPIRATORY DISTRESS SYNDROME;FLUID OVERLOAD;TOXICITY TO VARIOUS AGENTS	Life Threatening,Other Serious
10	7987819	2	JP-PFIZER INC-2011089935	12/2/2011	77	M	JPN	RENAL IMPAIRMENT	Disabled,Other Serious
11	8255195	1	CA-ROXANE LABORATORIES, INC.-2011-RO-01640RO	11/18/2011	61	F		NEUROLEPTIC MALIGNANT SYNDROME;RENAL FAILURE;ELECTROLYTE IMBALANCE;RESPIRATORY FAILURE;DEATH	Death,Life Threatening,Other Serious
12	8196352	2	GB-PFIZER INC-2011253012	11/8/2011	47	M	GBR	RHABDOMYOLYSIS	Death,Hospitalized
13	8200537	2	GB-PFIZER INC-2011254774	11/7/2011	18		GBR	RHABDOMYOLYSIS;RENAL FAILURE ACUTE	Hospitalized,Other Serious
14	8194926	2	GB-NAPPMUNDI-GBR-2011-0008930	11/3/2011	47	M	GBR	RHABDOMYOLYSIS	Death
15	8201195	2	GB-NAPPMUNDI-GBR-2011-0008935	11/3/2011	18		GBR	RHABDOMYOLYSIS	Hospitalized
16	8226354	1	GB-WATSON-2011-18010	11/3/2011	18		GBR	RHABDOMYOLYSIS;PNEUMONIA KLEBSIELLA;KLEBSIELLA BACTERAEEMIA	Other Serious

Table 7. Case Characteristics for adult patients with Vasopressin (N=88)									
	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
17	8226357	1	GB-WATSON-2011-18009	11/3/2011	47		GBR	RHABDOMYOLYSIS;ENTEROBACTER BACTERAEemia	Death,Other Serious
18	8226363	1	GB-WATSON-2011-18014	11/3/2011	35		GBR	RHABDOMYOLYSIS;ENTEROCOCCAL BACTERAEemia;STAPHYLOCOCCAL INFECTION	Other Serious
19	8176401	2	GB-TEVA-305864ISR	10/25/2011	47	M	GBR	MULTI-ORGAN FAILURE;RHABDOMYOLYSIS;RENAL FAILURE ACUTE	Death,Hospitalized,Other Serious
20	8135233	1	1019892	9/2/2011	68	M	CAN	HAEMORRHAGE	Death
21	8737337	1		8/5/2011	83	M	USA	PRODUCT QUALITY ISSUE	Other Serious
22	7930547	1		4/21/2011	51	F	USA	HAEMORRHAGIC ANAEMIA;PROCEDURAL HAEMORRHAGE;DRUG INEFFECTIVE	Hospitalized
23	7555212	1	US-ROXANE LABORATORIE S, INC.-2010-RO-01119RO	8/26/2010	71	F		Toxicity to various agents;MULTI-ORGAN DISORDER;DEATH;URINE OUTPUT DECREASED;HYPERLIPIDAEMIA;ACIDOSIS;PULMONAR Y OEDEMA;ANAEMIA;HYPONATRAEMIA;HYPOTENSION;I NCORRECT DRUG ADMINISTRATION DURATION;MENTAL STATUS CHANGES	Death,Life Threatening,Other Serious
24	7553947	1	IN-WATSON-2010-11337	8/25/2010	35	F	IND	DRUG INEFFECTIVE;CARDIAC ARREST;DRUG INTERACTION	Death
25	7535202	1	GXKR2010IN08 666	8/10/2010	35	F	IND	DRUG INEFFECTIVE;VASOCONSTRICTION;TRISMUS;RESUSC ITATION;MUSCLE RIGIDITY;CARDIAC ARREST;LOW CARDIAC OUTPUT SYNDROME	Death,Other Serious
26	7498141	1	632679	7/9/2010	35	F	IND	GENERAL PHYSICAL HEALTH DETERIORATION;CONDITION AGGRAVATED;PULSE ABSENT;DRUG EFFECT DECREASED;TREATMENT FAILURE;POST PROCEDURAL COMPLICATION;WRONG DRUG ADMINISTERED;ANURIA;OXYGEN SATURATION DECREASED;ACIDOSIS;AIRWAY PEAK PRESSURE INCREASED;LOSS OF CONSCIOUSNESS;MUSCLE RIGIDITY;CARDIAC ARREST;TRISMUS;HYPOPERFUSION	Death
27	7458770	1		7/2/2010	73	M	USA	INTESTINAL ISCHAEMIA;INTRA-ABDOMINAL HAEMATOMA;BLOOD PRESSURE DECREASED	Death,Life Threatening
28	7469087	1	JHP201000189	6/30/2010	35	F	IND	CARDIAC ARREST;PULSE ABSENT;OXYGEN SATURATION DECREASED;VASOCONSTRICTION;LOSS OF CONSCIOUSNESS;ACIDOSIS;LOW CARDIAC OUTPUT SYNDROME;NO THERAPEUTIC RESPONSE;MEAN ARTERIAL PRESSURE	Death

Table 7. Case Characteristics for adult patients with Vasopressin (N=88)									
Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome	
							DECREASED;TRISMUS;TREATMENT FAILURE;ANURIA;MUSCLE RIGIDITY;AIRWAY PEAK PRESSURE INCREASED		
29	7387626	1	20100179	5/7/2010	53	M	USA	URINE OUTPUT DECREASED;NO THERAPEUTIC RESPONSE;HYPONATRAEMIA;HYPERNATRAEMIA	Other Serious
30	7387641	1	20100180	5/7/2010	32	M	USA	DIABETES INSIPIDUS;HYPERNATRAEMIA	Other Serious
31	7387647	1	20100175	5/7/2010	30	F	JPN	PULSE ABSENT;ELECTROCARDIOGRAM ST SEGMENT DEPRESSION;HEART RATE DECREASED;VENTRICULAR ARRHYTHMIA;HYPOTENSION;INCORRECT ROUTE OF DRUG ADMINISTRATION	Life Threatening,Other Serious
32	7370444	2	JHP201000126	4/27/2010	56	M	USA	RENAL FAILURE ACUTE;GENERAL PHYSICAL HEALTH DETERIORATION;CONTINUOUS HAEMODIAFILTRATION;PNEUMONIA;METABOLIC ACIDOSIS;SEPTIC SHOCK;CARDIAC ARREST;FLUID OVERLOAD;INFECTION;HYPERKALAEMIA	Death
33	7369115	1	JHP201000129	4/16/2010	34	F	IND	GRAND MAL CONVULSION;RADIAL PULSE ABNORMAL;HYPERTENSION;SINUS BRADYCARDIA;PALLOR;OFF LABEL USE;PULMONARY OEDEMA;TACHYCARDIA;UNRESPONSIVE TO STIMULI	Other Serious
34	7261054	1	US-BAXTER-2010BH001211	1/29/2010	77	F	USA	DEATH;INCORRECT DOSE ADMINISTERED;OVERDOSE	Death,Life Threatening,Other Serious
35	7213970	1		12/14/2009	63	M	USA	SEPSIS;ACUTE RESPIRATORY DISTRESS SYNDROME	Death
36	7199151	1	JHP200900353	11/19/2009	86	F	USA	RESPIRATORY FAILURE;POST PROCEDURAL HAEMORRHAGE;CARDIOGENIC SHOCK	Life Threatening,Other Serious
37	7153443	1	20090425	10/6/2009	32	M	USA	HYPERNATRAEMIA;DIABETES INSIPIDUS	Other Serious
38	7125182	1	US-BAXTER-2009BH014159	9/22/2009	83	F	USA	VENTRICULAR TACHYCARDIA;DEATH;CARDIAC ARREST	Death,Life Threatening
39	7077039	1	US-ROXANE LABORATORIE S, INC.-2009-RO-00784RO	8/10/2009	65	F		HYPOTENSION;CONVULSION;RHYTHM IDIOVENTRICULAR;PULMONARY EMBOLISM;POOR PERIPHERAL CIRCULATION;LEFT VENTRICULAR HYPERTROPHY;Hypoxic-ischaemic encephalopathy;Pulseless electrical activity;CARDIOGENIC SHOCK;HYPOPERFUSION;CARDIAC FAILURE;PERIPHERAL ISCHAEMIA;BRADYCARDIA;VENTRICULAR TACHYCARDIA;Toxicity to various agents;CARDIO-	Hospitalized,Other Serious

Table 7. Case Characteristics for adult patients with Vasopressin (N=88)									
Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome	
							RESPIRATORY ARREST;OVERDOSE		
40	6996186	1		5/11/2009	70	M	USA	DRUG EFFECT DECREASED	Other Serious
41	6928815	2	JHP200900021	2/26/2009	30	F	JPN	HYPOTENSION;VENTRICULAR EXTRASYSTOLES;ELECTROCARDIOGRAM ST SEGMENT DEPRESSION;HEART RATE DECREASED;HEART RATE INCREASED;BLOOD PRESSURE INCREASED	Life Threatening
42	6640368	2	US-PFIZER INC-2008040233	5/27/2008	22	F	USA	PERIPHERAL ISCHAEMIA;RENAL FAILURE ACUTE;HYPOTENSION;SUICIDE ATTEMPT;INTENTIONAL OVERDOSE;RESPIRATORY FAILURE;OCCULT BLOOD POSITIVE;ATRIOVENTRICULAR BLOCK COMPLETE	Hospitalized,Other Serious
43	6130889	5	JP-MERCK-0609USA02962	11/28/2006	77	M	JPN	PANCREATIC NECROSIS;TOXIC EPIDERMAL NECROLYSIS;RHABDOMYOLYSIS;SEPTIC SHOCK;STAPHYLOCOCCAL INFECTION;ADRENAL CORTEX NECROSIS;PNEUMONIA;ACUTE RESPIRATORY DISTRESS SYNDROME;MULTI-ORGAN FAILURE	Death,Other Serious
44	5928150	1	US-KINGPHARMU SA00001-K200501490	11/23/2005	34	M	USA	HYPERNATRAEMIA;POLYURIA;IATROGENIC INJURY;DIABETES INSIPIDUS	Hospitalized
45	5884287	1	CA-KINGPHARMU SA00001-K200501209	9/23/2005	31	F	CAN	BRADYCARDIA;HEART RATE DECREASED;BLOOD PRESSURE DECREASED;ATRIOVENTRICULAR BLOCK;HYPERTENSION;EXTRASYSTOLES;HAEMORRHAGE;Supraventricular extrasystoles;OXYGEN SATURATION IMMEASURABLE;BLOOD PRESSURE IMMEASURABLE;PULSE ABSENT	Hospitalized
46	5800618	1	TW-KINGPHARMU SA00001-K200500601	5/20/2005	81	M		MULTI-ORGAN FAILURE;VENTRICULAR HYPOKINESIA;BLOOD CREATININE INCREASED;ABDOMINAL DISTENSION;HEPATIC ENZYME INCREASED;ASPARTATE AMINOTRANSFERASE INCREASED;Amylase increased;AIR EMBOLISM;ALANINE AMINOTRANSFERASE INCREASED;AORTIC ARTERIOSCLEROSIS;INTESTINAL INFARCTION;NECROTISING COLITIS;Pneumatosis intestinalis;EJECTION FRACTION DECREASED	Death

	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
47	5734933	1	05H-163-0287549-00	1/31/2005	53	M	USA	BLINDNESS UNILATERAL;OPTIC ISCHAEMIC NEUROPATHY	Disabled
48	5734945	1	05H-163-0287546-00	1/31/2005	50	M	USA	OPTIC NEUROPATHY;PUPILLARY REFLEX IMPAIRED;BLINDNESS;INJURY;OPTIC ISCHAEMIC NEUROPATHY;FACIAL BONES FRACTURE	Disabled
49	5734948	1	05H-163-0287528-00	1/31/2005	58	M	USA	OPTIC ISCHAEMIC NEUROPATHY;INJURY;BLINDNESS	Disabled
50	5734951	1	05H-163-0287551-00	1/31/2005	50	F	USA	OPTIC ISCHAEMIC NEUROPATHY;BLINDNESS	Disabled
51	5709368	1	2004-DE-06154GD(0)	12/27/2004	19	F	USA	CARDIAC ARREST;ANAPHYLACTIC REACTION;RESPIRATORY DISTRESS;RESPIRATORY ARREST;DRUG INEFFECTIVE	Life Threatening, Other Serious
52	5711307	1	04H-163-0282577-00	12/27/2004	66	M	USA	SINUS ARRHYTHMIA;CARDIAC ARREST;ELECTROENCEPHALOGRAM ABNORMAL;BLOOD PRESSURE DECREASED	Life Threatening
53	4189955	1	K200401084	8/4/2004	53	M	USA	HYPERNATRAEMIA;DIABETES INSIPIDUS;BLOOD SODIUM DECREASED;DRUG INEFFECTIVE	Hospitalized
54	4056804	2	200314804FR	1/15/2004	71	M	FRA	CARDIO-RESPIRATORY ARREST;SKIN NECROSIS;THROMBOCYTOPENIC PURPURA;SCROTAL ULCER	Death,Hospitalized
55	4036281	1	K200301756	11/14/2003	94	M	USA	INJECTION SITE ERYTHEMA;GASTROINTESTINAL HAEMORRHAGE	Death
56	4034747	1	K200301747	11/12/2003	67	M	GBR	HYPOGLYCAEMIA;COMPUTERISED TOMOGRAPH ABDOMEN ABNORMAL;CYANOSIS;INTESTINAL INFARCTION;DRUG INEFFECTIVE;DIALYSIS;ATRIAL FIBRILLATION;LACTIC ACIDOSIS;GENERAL PHYSICAL HEALTH DETERIORATION;MEAN ARTERIAL PRESSURE DECREASED;ALANINE AMINOTRANSFERASE INCREASED;BLOOD ALKALINE PHOSPHATASE INCREASED	Death
57	4031198	1	2003113501	11/3/2003	78	F	DEU	SHOCK;BLOOD CREATININE INCREASED;COMPLETED SUICIDE;INTESTINAL ISCHAEMIA;OVERDOSE;TOXICITY TO VARIOUS AGENTS;VASODILATATION	Death,Hospitalized, Other Serious
58	3988399	1		8/14/2003	40	M	USA	MEDICATION ERROR;HYPOVOLAEMIA	Death
59	3979997	1		7/28/2003	44	F	USA	MEDICATION ERROR	Other Serious
60	3935166	1		4/16/2003	50	M	USA	PERIPHERAL ISCHAEMIA;FINGER AMPUTATION;DRY GANGRENE;NECROSIS ISCHAEMIC	Hospitalized

Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome	
61	3858663	2	2002055810	12/23/2002	25	F	USA	CANDIDIASIS;BLOOD PRESSURE DECREASED;ALANINE AMINOTRANSFERASE INCREASED;BILIRUBIN CONJUGATED INCREASED;HYPOKALAEMIA;HYPOMAGNEAEMIA;LOSS OF CONSCIOUSNESS;VENTRICULAR TACHYCARDIA;DRUG LEVEL INCREASED;HAEMODYNAMIC INSTABILITY;DRUG INTERACTION;NAUSEA;BLOOD BILIRUBIN INCREASED;ELECTROCARDIOGRAM T WAVE INVERSION;RESPIRATORY RATE INCREASED;BENIGN HEPATIC NEOPLASM;POSTOPERATIVE FEVER;PYREXIA;HEPATOMEGALY;TORSADE DE POINTES;BRADYCARDIA	Other Serious
62	3721920	2	200121395GDD C	10/15/2001	52	M	JPN	ANGINA PECTORIS;MUSCLE SPASMS	Other Serious
63	3387460	1		11/19/1999	40	F	USA	CARDIAC ARREST;PULMONARY OEDEMA	Hospitalized,Life Threatening
64	3167292	1	PTR-90081198	11/18/1998	31	F	USA	PARALYSIS;CEREBROVASCULAR ACCIDENT	Hospitalized,Disabled
65	3069220	1	0810106970003	10/1/1997	70	M	JPN	APNOEA;HEPATIC ENCEPHALOPATHY;RHABDOMYOLYSIS;HEPATIC NEOPLASM MALIGNANT	Death,Hospitalized, Other Serious
66	3047459	1	0010106970004	9/5/1997	33	F	USA	RHABDOMYOLYSIS;BLOOD CREATINE PHOSPHOKINASE INCREASED	Hospitalized,Other Serious
67	5612163	1	0010106970005	9/5/1997	22	F	USA	DRUG INTERACTION;VENTRICULAR EXTRASYSTOLES;HYPOTENSION;BRADYCARDIA	Life Threatening
68	5608886	1	0020106970001	8/19/1997	24	F	CAN	HYPOTENSION;PULMONARY OEDEMA;ATRIOVENTRICULAR BLOCK;BRADYCARDIA	Hospitalized,Life Threatening
69	5608902	1	0810106970002	8/19/1997	73	M	JPN	BLOOD CREATINE PHOSPHOKINASE INCREASED;RHABDOMYOLYSIS;MYASTHENIC SYNDROME;MYOPATHY	Death,Hospitalized
70	5545169	1	0010106970002	3/28/1997	30	F	USA	HYPOTENSION;BRADYCARDIA	Life Threatening
71	5479376	1		11/5/1996	67	M	USA	INJECTION SITE NECROSIS;DERMATITIS EXFOLIATIVE;ECCHYMOSIS;INJECTION SITE REACTION	Other Serious
72	5460220	1	0010106960002	10/22/1996	74	F	USA	HYPOCALCAEMIA;HYPONATRAEMIA;HYPOCHLORAEMIA;HYPOKALAEMIA	Hospitalized

	Case #	Version	Manufacturer Control #	FDA Received Date	Age (Yrs)	Sex	Country	Preferred Terms (PTs)	Outcome
73	5466128	1	420150	10/8/1996	22	F	USA	DRUG INTERACTION;BRADYCARDIA;VENTRICULAR EXTRASYSTOLES;HYPOTENSION	Life Threatening, Other Serious
74	5428523	1	8860106960001	7/26/1996	35	M	TWN	HYPOXIA;LUNG DISORDER;PULMONARY OEDEMA;DYSNPOEA	Hospitalized
75	5403842	1	0810106960002	5/10/1996	55	M	JPN	PNEUMONIA;HYPONATRAEMIA;NEUROPATHY PERIPHERAL	Death, Hospitalized
76	5398255	1		4/8/1996	53	M	USA	SKIN HYPERTROPHY;INJECTION SITE REACTION;DERMATITIS EXFOLIATIVE	Hospitalized, Other Serious
77	5227973	1	35312	3/30/1995	35	F	USA	BLOOD CREATINE PHOSPHOKINASE INCREASED;MYOCARDIAL INFARCTION	Hospitalized
78	5167835	1	32400	10/3/1994	39	F	USA	HYPOTENSION;PARAESTHESIA;ARTERIAL OCCLUSIVE DISEASE;ALOPECIA	Hospitalized
79	5105790	1	29589	4/18/1994	52	M	ESP	MYOPATHY;PURPURA;SEPSIS;SKIN NECROSIS	Death, Hospitalized
80	5105047	1	29505	4/6/1994	46	M	JPN	BLOOD CREATININE INCREASED;MYOPATHY;RENAL FAILURE;BLOOD CREATINE PHOSPHOKINASE INCREASED	Hospitalized
81	5081925	1		2/18/1994	68	M	USA	CHILLS;ATRIOVENTRICULAR BLOCK SECOND DEGREE	Life Threatening
82	5098311	1		2/15/1994	68	M	USA	CHILLS;ATRIOVENTRICULAR BLOCK SECOND DEGREE;ATRIOVENTRICULAR BLOCK FIRST DEGREE	Life Threatening
83	5043912	1	26815	10/19/1993	74	M	JPN	VARICOSE VEIN;BLOOD CREATINE PHOSPHOKINASE INCREASED;OESOPHAGEAL HAEMORRHAGE;MYOPATHY	Death, Hospitalized
84	5026055	1	26023	9/2/1993	51	M	JPN	PURPURA;HEPATIC FUNCTION ABNORMAL;RENAL FAILURE ACUTE;MYOPATHY	Death, Hospitalized
85	5021410	1	25358	7/29/1993	49	M	JPN	HYPONATRAEMIA;TREMOR;PERSONALITY DISORDER	Hospitalized
86	5014049	1	25212	7/26/1993	52	M	ESP	INFECTION;MYOPATHY;BLOOD CREATINE PHOSPHOKINASE INCREASED;TOXIC EPIDERMAL NECROLYSIS	Death, Hospitalized
87	5010164	1	24039	6/23/1993	65	M	ESP	MYOPATHY;PARAESTHESIA;SKIN NECROSIS	Hospitalized
88	4864340	1	924200003	4/2/1992	60	M	USA	ATRIAL FIBRILLATION;RESPIRATORY DISORDER	Death

U=Unknown; Country Codes: JPN=Japan; GBR=United Kingdom; AUT=Australia; CAN=Canada; IND=India; FRA=France; DEU=Germany; TWN=Taiwan; ESP=Spain; USA=United States of America

APPENDIX

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data 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 reports for every adverse event or medication error that occurs 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, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

OSE uses Empirica Signal software, which uses the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm, to perform analyses on FAERS data and identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. MGPS analyzes the records in FAERS 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 FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data.

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

/s/

MARK S MILLER
01/22/2013

SUSAN LU
01/22/2013

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

INSTRUCTIONS FOR COMPLETING THE SRPI

There is one drop-down menu and one comment field for each item.

Drop-Down Menu: “NO” is the default option. For each SRPI item, click on the word “NO” and choose one of three following options:

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

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word “Comment” and insert your comment.

INSTRUCTIONS FOR COPYING ITEMS FROM SRPI TO 74-DAY OR ADVICE LETTER:

The SRPI is “protected” (or “locked”) to allow use of the drop-down menus. However, the “protection” mode does not allow you to directly copy the SRPI item into the 74-day or advice letter.

To copy SRPI items in the letter, after completion of the 48-item SRPI checklist, unprotect (or unlock) the document:

Microsoft Word 2003

(1) Click on the “Tools” tab, then (2) click on “Unprotect Document.”

Microsoft Word 2007

(1) Click the “Review” tab, (2) click on “Protect Document”, (3) on “Restrict Formatting and Editing” window click “Stop Protection” at the bottom of the window, and (3) click “OK” (leave the password box blank).

If you need to switch from the “unprotected” mode back to the “protected” mode to allow use of the drop-down menus:

Microsoft Word 2003

(1) Click the “Tools” tab (2) click on “Protect Document”, (3) click on “Yes, Start Enforcing Protection” in the right-sided task pane, and (4) click “OK” (leave the password box blank).

Microsoft Word 2007

(1) Click the “Review” tab, (2) click on “Protect Document” tab, (3) click on “Restrict Formatting and Editing”, (4) click on “Yes, Start Enforcing Protection”, and (5) click “OK” (leave the password box blank).

END INSTRUCTION: DELETE ALL INSTRUCTIONS BEFORE DARRTS CHECK-IN.]

Selected Requirements of Prescribing Information (SRPI)

Highlights (HL)

GENERAL FORMAT

- NO** 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: Margins must be 1/2 inch on all sides and they are not. We recommend that the applicant use 8-point to meet the ½ page length requirement for the Highlights.

- NO** 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: The length of HL must be less than or equal to one-half page and it is not. Sponsor has not submitted a waiver request of the one-half page requirement.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

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

Comment:

- 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: In INDICATIONS AND USAGE, the numerical identifier for "Septic shock" should be "(1.3)" not "(b)(4)" as proposed. Additionally, the statement "(b)(4)n® is incompatible with 5% dextrose (D5W) and this diluent should NOT be used to dilute (b)(4)n®." should have an identifier (2).

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

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

Selected Requirements of Prescribing Information (SRPI)

• 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

NO

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: *The HL Limitation Statement should be located on the line immediately beneath the HL heading and it is not. The name proprietary name should be in UPPER CASE in both sentences and it is not.*

Product Title

YES

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

Comment:

Initial U.S. Approval

NO

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: *Initial U.S. Approval in HL must be placed immediately beneath the product title and it is not.*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

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

- N/A** 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 class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- 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:

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:

- NO** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *There is more than one contraindication and each contraindication should be bulleted, but it is not.*

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:

Selected Requirements of Prescribing Information (SRPI)

- NO** 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:** The INDICATIONS AND USAGE section in the FPI has three subsections (1.1, 1.2, and 1.3), but the CONTENTS only lists 1.1 and 1.2. The ADVERSE REACTIONS section in the FPI has 3 subsections (6.1, 6.2, and 6.3), but these are not listed in CONTENTS. The CLINICAL PHARMACOLOGY section in the FPI has 3 subsections (12.1, 12.2, and 12.3), but these are not listed in CONTENTS. The CLINICAL STUDIES section in the FPI has 4 subsections (14.1, 14.2, 14.3, and 14.4), but these are not listed in CONTENTS.*
- 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**.
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

- NO** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment: *The sponsor has italicized this heading and it should be un-italicized.*
- 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

Selected Requirements of Prescribing Information (SRPI)

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
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:

- N/A** 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:

Selected Requirements of Prescribing Information (SRPI)

- 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

- NO** 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:

“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: Sponsor should re-title Section 6.1 to “Clinical Trials Experience.” Sponsor should include the relevant limitation statement in this section. Section 6.1 includes any adverse reactions from studies, including Phase 3 trials and open-label studies.

- NO** 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: Sponsor should re-title Section 6.2 to “Postmarketing Experience.” Sponsor should include the relevant limitation statement in this section. Section 6.2 includes adverse reactions from voluntary, spontaneous reports (from AERS).

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/

QUYNH M NGUYEN
12/06/2012

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 # 204-485 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Pitressin Established/Proper Name: vasopressin injection, USP Dosage Form: Injection Strengths: 20 units/mL		
Applicant: JHP Pharmaceuticals, LLC Agent for Applicant (if applicable):		
Date of Application: 9-25-12 Date of Receipt: 9-26-12 Date clock started after UN:		
PDUFA Goal Date: 7-26-13		Action Goal Date (if different):
Filing Date: 11-25-12		Date of Filing Meeting: 11-8-12
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed indication(s)/Proposed change(s): Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.		
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” review 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 (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <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 (<i>if OTC product</i>):				
List referenced IND Number(s): Pre-IND 112,944				
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 New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.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		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<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 505(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 1457 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>		
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 314.108(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? Check the Orphan Drug Designations and Approvals list at: 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>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</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>NDA 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>				

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 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>NDA/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 #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
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			
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			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <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 FD&C Act 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>	X			
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	
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

PREA	X			
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <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>		X		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver request included in NDA.
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 CDER OSI RMP 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			

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

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

	<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 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>				

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

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)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Pre-NDA Telecon with DCRP on 10-17-11 Pre-NDA Telecon with DMEP on 10-17-11	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-8-12

BLA/NDA/Supp #: 204485

PROPRIETARY NAME: Pitressin

ESTABLISHED/PROPER NAME: Vasopressin Injection, USP

DOSAGE FORM/STRENGTH: 20 units/mL

APPLICANT: JHP Pharmaceuticals, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

BACKGROUND: JHP Pharmaceuticals submitted this 505(b)(2) NDA for Pitressin (vasopressin injection, USP), (b) (4) Pitressin is a marketed, unapproved product, which, according to the sponsor, has been available on the market for over 98 years for the treatment of diabetes insipidus. The sponsor states that it is a pre-1938 drug and therefore categorized as a grandfathered product, manufactured and marketed by various companies without the approval of an NDA.

The proposed indication is for treatment of vasodilatory shock, including post-cardiotomy shock and septic shock. The sponsor has submitted a literature-based NDA as per discussion at the October 17, 2011 Pre-NDA Teleconference with DCRP (Pre-IND 112,944). (b) (4)

According to the sponsor's Pre-NDA meeting package dated September 11, 2011, JHP Pharmaceuticals' Pitressin drug product is composed of vasopressin, which is the same drug that was historically marketed by Parke-Davis. Through a series of transactions, JHP has acquired the manufacturing site in Rochester, MI, the trademark, and all intellectual property (including know-how) associated with the Pitressin drug product, previously manufactured and marketed by Parke-Davis.

According to DAARTS, two NDAs for Pitressin were submitted by Parke-Davis and reviewed in DMEP. NDA 3402 for Pitressin Tannate in Oil Injection was approved in 1941. The product was subsequently withdrawn from marketing (NDA "withdrawn FR effective" on September 25, 1998). NDA 19286 for Pitressin Injection was "withdrawn" on December 13, 1984.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Monica Fiszman	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:	Peter Hinderling	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Fanhui Kong	Y
	TL:	James Hung	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rama Dwivedi	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lyudmila Soldatova Elsbeth Chikhale (Biopharm)	Y Y
	TL:	Kasturi Srinivasachar Angelica Dorantes (Biopharm)	Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erica Pfeiler	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Appears This Way On Original

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Norman Stockbridge, Sally Loewke (OND IO)		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <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
<p>CLINICAL</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 study site(s) inspections(s) needed? <p>If no, explain: This NDA is based solely on the literature. The MO and CDTL agreed that an inspection was not needed.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p>	<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>this drug/biologic is not the first in its class</i> ○ <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 checked="" 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

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Appears This Way On Original

<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 checked="" 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 style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">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:</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>	<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

CMC Labeling Review	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 2-25-13	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> • 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"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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
12/04/2012