

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204485Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



870 Parkdale Road
Rochester, MI 48307

Debarment Certification

This is to certify that JHP Pharmaceuticals LLC (JHP) did not and will not use in any capacity the services of any person debarred under Section 306 subpart (a) or (b) of the Generic Drug Enforcement Act of 1992 and the Federal Food Drug and Cosmetic Act in connection with the manufacturing or testing of pharmaceutical products.

JHP also declares that no one responsible for the development or submission of an ANDA/NDA/NADA has been convicted of a crime as defined by Section 306 subpart (a) or (b) within the last 5 years.

A handwritten signature in black ink, appearing to read 'Adetayo O. Adebisi', is written over a horizontal line.

Adetayo O. Adebisi
Director, Compliance

A handwritten date 'October 26, 2011' is written in black ink over a horizontal line.

Date

EXCLUSIVITY SUMMARY

NDA # 204-485

SUPPL #

HFD # 110

Trade Name Vasostrict

Generic Name vasopressin injection, USP

Applicant Name Par Sterile Products, LLC

Approval Date, If Known 4-17-14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) This NDA is based solely on the published literature.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Discontinued NDA

NDA# 3-402

Pitressin tannate (vasopressin tannate) Injection

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Quynh Nguyen, PharmD, RAC
Title: Regulatory Project Manager, Division of Cardiovascular and Renal Products
Date: 4-17-14

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

QUYNH M NGUYEN
04/17/2014

NORMAN L STOCKBRIDGE
04/17/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204-485 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vasostrict Established/Proper Name: vasopressin, USP Dosage Form: Injection		Applicant: Par Sterile Products, LLC Agent for Applicant (if applicable):
RPM: Quynh Nguyen, PharmD, RAC		Division:
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 4-17-14 </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>4-18-14</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None CR on 7-19-13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): AP on 4-17-14; CR on 7-19-13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	3-6-13
• Review(s) (<i>indicate date(s)</i>)	2-6-14; 3-6-13
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 12-6-12 DMEPA: <input type="checkbox"/> None 4-8-14; 2-27-14; 2-14-14; 6-7-13 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 5-29-13 SEALD: <input type="checkbox"/> None 4-3-13 CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None PMHS: 5-24-13
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	4-17-14; 7-19-13; 12-4-12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 3-20-14; 6-10-13
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>5-8-13</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 10-17-11
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-4-14; 7-18-13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-27-14; 6-13-13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	2-21-14; 5-25-13; 12-4-12
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	5-25-13 (see p.11 of Dr. Fiszman's Clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 1-22-13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review (signed the primary review 5-29-13)
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5-29-13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review (signed the primary reviews 5-24-13; 5-28-13; 11-8-12)
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5-24-13; 11-8-12
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review (signed the primary reviews 4-10-13; 10-31-12)
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-10-13; 10-31-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review (signed the primary reviews 4-8-14; 3-18-14; 5-9-13; 3-15-13; 11-8-12; 11-5-12)
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4-8-14; 3-18-14; 5-8-13; 3-15-13; 11-8-12; 11-5-12
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 12-3-13; 4-8-13; 11-8-12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	3-18-14; 5-9-13 CMC reviews
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 4-4-14(see 4-8-14 CMC Memo for EER printout) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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
04/23/2014



NDA 204485

**ACKNOWLEDGE CORPORATE
NAME CHANGE**

Par Sterile Products, LLC
Attention: Mr. Steve Richardson
VP, Scientific & Regulatory Affairs
One Upper Pond Road, Bldg. D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Richardson:

We acknowledge your March 4, 2014 correspondence notifying the Food and Drug Administration (FDA) that Par Pharmaceutical Companies, Inc. acquired JHP Pharmaceuticals, LLC and the corporate name has been changed from

JHP Pharmaceuticals, LLC

to

Par Sterile Products, LLC

for NDA 204485 for Vasostrict (vasopressin injection, USP) (b) (4), 1 mL vial
(20 pressor units).

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
03/19/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204485

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

JHP Pharmaceuticals, LLC
Morris Corporate Centre 2
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

ATTENTION: Gerald Vasquez
Manager, Regulatory Affairs

Dear Mr. Vasquez:

Please refer to your Class 2 Resubmission, dated and received, October 18, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vasopressin Injection, USP, 20 Units per mL.

We also refer to your correspondence, dated and received November 18, 2013, requesting review of your proposed proprietary name, Vasostrict. We have completed our review of the proposed proprietary name, Vasostrict, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 18, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Quynh Nguyen, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
02/11/2014



NDA 204485

INFORMATION REQUEST

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA 204-485) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pitressin (vasopressin) Injection.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the proposed drug product specifications
 - i. The acceptance criterion of (b) (4) – (b) (4) % for shelf-life assay is not acceptable. Therefore, revise the acceptance criterion for shelf-life assay from (b) (4) – (b) (4) % to (b) (4) – (b) (4) % (from (b) (4) U/ml to (b) (4) U/ml).
 - ii. Your justification of the shelf life acceptance criteria of (b) (4) % for impurity (b) (4) is not supported by the provided stability data. Reduce the shelf life acceptance criteria for impurity (b) (4) to NMT (b) (4) %.
 - iii. Revise the drug product specifications to correct the name for (b) (4), which was not identified to the correct name, (b) (4).
 - iv. Amend your NDA with the updated drug product specification and submit a revised drug product specification table.
2. Analytical method 20545 is not validated for adequate quantification of impurity (b) (4) in Pitressin. Optimize HPLC Method 20545 to be capable of quantifying impurity (b) (4) at a level of NMT (b) (4) %. Include validation data for the optimized method to demonstrate its suitability to quantify the (b) (4) impurity. Provide the level of (b) (4) in the primary stability batches at the current time point of stability studies using your optimized method.
3. Provide Development Report 13022 that is mentioned in regard to the levels of impurity (b) (4)

4. Provide the chemistry stability data (assay and impurities) supporting statement that Pitressin is compatible with dextrose 5% as indicated in the Amendment dated May 05, 2013.
5. You have stated that the test and acceptance criteria for individual specified and unspecified impurities are included in the drug substance specification, however, the updated specification does not contain this information. Provide the updated drug substance specification that includes the test and acceptance criteria for individual specified and unspecified impurities.

Labeling: Vials and Container Labels

6. Remove the following statement on the carton label: [REDACTED] (b) (4)
7. Revise the storage temperature on the carton label to the following: “Store between 15°C and 25°C (59°F and 77°F)”.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
02/07/2014



NDA 204485

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

We acknowledge receipt on October 18, 2013, of your October 18, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pitressin (vasopressin) Injection, 1 ml vial (20 pressor units).

We consider this a complete, class 2 response to our July 19, 2013 action letter. Therefore, the user fee goal date is April 18, 2014.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
11/12/2013



NDA 204485

**PROPRIETARY NAME REQUEST
WITHDRAWN**

JHP Pharmaceuticals, LLC
Morris Corporate Centre 2
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

ATTENTION: Gerald Vasquez
Manager, Regulatory Affairs

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vasopressin Injection, USP, 20 Units per mL.

We acknowledge receipt of your correspondence, dated and received on June 24, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of June 24, 2013.

We note that you indicated in your submission dated May 17, 2013, that you intend to submit an alternate proprietary name, Vasostrict, for this application. In order to initiate the review of the alternate proprietary name, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Quynh Nguyen, at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/05/2013



NDA 204485

LABELING PMR/PMC DISCUSSION COMMENTS

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pitressin (vasopressin) Injection, 1 ml vial (20 pressor units).

We also refer to our December 7, 2012 letter in which we notified you of our target date of June 26, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

CONTENT OF LABELING

On May 5, 2013, we received your May 3, 2013 updated proposed labeling submission to this application, and we propose revisions that are included as an enclosure.

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

On May 20, 2013, we received your May 17, 2013 updated proposed labeling submission to this application, and we propose the following revisions:

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 1-6 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. 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.
4. 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.

Submit draft carton and container labeling revised as described above.

POSTMARKETING REQUIREMENT

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.

Please provide a response to these labeling and Postmarketing Requirement comments by July 3, 2013.

If you have any questions, please contact me at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Revised labeling for Content of Labeling

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

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/s/

QUYNH M NGUYEN
06/26/2013

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 12, 2013

TIME: 12:30 pm - 1:00 pm

LOCATION: WO Bldg 22,

DRUG NAME: NDA 204485 (b) (4)

TYPE OF MEETING: Teleconference with JHP Pharma.

MEETING RECORDER: Cherye Milburn, SRPM, OSE

FDA ATTENDEES:

Irene Z. Chan, TL DMEPA, OSE

Kimberly DeFronzo, Safety Evaluator, DMEPA, OSE

Karen Bengtson, SRPM, OSE

EXTERNAL ATTENDEES:

Mark Tran-Senior Product Manager

Steve Richardson-VP Regulatory and Scientific Affairs

Gerald Vasquez-Senior Manager Regulatory Affairs

Background:

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.

On May 20, 2013, a request for proprietary name review was received for (b) (4) as the primary name with an alternate name of VasoStrict.

Meeting Objectives:

DMEPA requested this teleconference to inform JHP Pharma of our preliminary concerns with the primary proposed proprietary name, (b) (4). DMEPA wants to emphasize that the alternate name, VasoStrict, is not under formal review since DMEPA only reviews one name at a time. However, we preliminarily looked at VasoStrict in order to give you feedback for today's teleconference.

Discussion:

1. (b) (4)

(b) (4)

(b) (4)

(b) (4)

2. VasoStrict

Capital letter is in the name

The name VasoStrict also contains a capital letter (“S”) in the middle of the name. Thus, similar to our recommendation with (b) (4) the use of tall-man lettering in a proposed proprietary name is inappropriate and should not be used.

Regulatory Options:

1. Wait for DMEPA to complete the review and issue a denial letter for the proprietary name (b) (4) by the OSE PDUFA goal date of 8/18/13, which differs from the OND application goal date of 7/26/13.
2. Withdraw the proposed name (b) (4) and submit another name for our review.

Action Items:

JHP Pharma will send in a withdrawal letter for the proposed name (b) (4)

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/s/

CHERYE D MILBURN
06/17/2013

Duggan, Leora

From: Duggan, Leora
Sent: Wednesday, April 10, 2013 2:42 PM
To: 'Vasquez, Gerald'
Cc: McKnight, Rebecca
Subject: RE: IR Question for NDA 204485

Dear Mr. Vasquez,

The excel file is acceptable with the data format that was provided in the Comment #18 of the IR Letter dated 03/07/2013. Please submit the information to me via email, and as a formal amendment to your application.

Best Regards,

Leora Duggan, PMP
Regulatory Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
CDER, FDA
Phone (240) 402 – 3777
Fax: (301) 796 – 9749

From: Vasquez, Gerald [<mailto:Gerald.Vasquez@JHPPHARMA.COM>]
Sent: Tuesday, April 09, 2013 2:59 PM
To: Duggan, Leora
Cc: McKnight, Rebecca
Subject: RE: IR Question for NDA 204485

Dear Ms. Duggan,

We thank you for your email and at the same time acknowledge the request for a response to Comment #18 by COB Friday 4/12/2013.

We would also like to inform you that presently JHP does not have a SAS data system for reporting stability information. A such, would an excel file with the relevant information be acceptable? Please advise.

I look forward to your response and guidance.

Regards,

Gerald Vasquez

Manager, Regulatory Affairs

JHP Pharmaceuticals, LLC
Morris Corporate Centre 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Office: (973) 658-3551

Fax: (973) 658-3585

email: gerald.vasquez@jhppharma.com

web: www.jhppharma.com

From: Duggan, Leora [<mailto:Leora.Duggan@fda.hhs.gov>]

Sent: Tuesday, April 09, 2013 10:21 AM

To: Vasquez, Gerald

Cc: McKnight, Rebecca

Subject: IR Question for NDA 204485

Dear Mr. Vasquez,

We are reviewing NDA 204485 and have the following information request:

To expedite the review process, please send the response to Comment #18 of the IR Letter dated 03/07/2013, as early as possible. This response can be submitted before the responses to the other questions. Please include the SAS data for the updated 9-month stability results submitted in the Amendment dated 03/07/2013.

Please respond via email to me and as a formal amendment to the application by COB Friday, 4/12/2013.

Best Regards,

Leora Duggan, PMP
Regulatory Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
CDER, FDA
Phone (240) 402 – 3777
Fax: (301) 796 – 9749

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/s/

LEORA F DUGGAN
05/10/2013



NDA 204485

INFORMATION REQUEST

JHP Pharmaceuticals, LLC
Attention: Gerald Vasquez, Manager, Regulatory Affairs
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasopressin Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. The (b) (4) DMF (b) (4) that you are referencing for vasopressin synthesis is currently deficient. A Deficiency Letter dated February 22, 2013 was sent to DMF holder. In order to have an approval of the submitted NDA, the DMF (b) (4) should receive an adequate status.
2. The proposed specification for Vasopressin is not sufficient for release of drug substance. Include the following tests and acceptance criteria in the specification: identification by amino acid analysis, specific optical rotation, each specified identified impurity with the proposed acceptance criteria and any unidentified impurity with the proposed limit, peptide content, heavy metals and total microbial aerobic count.
3. Include acceptance criteria for Identification A and Identification B in the drug substance specification.
4. To prove the proper structure of the vasopressin with disulfide bridge, conduct a bioassay as one-time characterization study of vasopressin, and correlate it with the HPLC test method used for the assay.
5. Optimize HPLC Method 20456 for Assay and Ordinary Impurities to be capable of resolution, detection and quantification of specified identified and unidentified impurities. Provide relative retention time for these impurities, and chromatograms that demonstrate resolution of individual impurities. Include validation of this method for suitability of determination of individual vasopressin impurities.
6. Provide description and validation of additional non-compendial analytical methods requested for complete specification for drug substance Vasopressin.

7. Explain decrease in Total Impurities from (b) (4) during (b) (4) year for vasopressin batch VP1002-1 shown in JHP’s Certificate of Analysis (COA) compared to (b) (4) COA. Explain increase in Assay levels of batches VP1001 and VP1002-1 shown in JHP’s COAs (b) (4) and compared to (b) (4) COAs (b) (4).

Drug Product

8. Include a test and acceptance criterion for pH in the (b) (4) during Pitressin manufacture.
9. Include an additional acceptance criterion for the Description test in the drug product specifications as follows: “Essentially free of visible particulates”.
10. Revise limit of NLT (b) (4) ml to NLT (b) (4) ml for “Volume in Container” Test for 3 ml multi-dose vials in the drug product specifications as per requirement of USP <1> for multi-dose containers.
11. The acceptance criterion of (b) (4) – (b) (4) % for shelf-life assay is not acceptable; it should comply with that of USP monograph for Vasopressin Injection.
12. Identification by HPLC retention time in the drug product specification is not specific. Include either a specific test, e.g., molecular mass by mass-spectrometry or another non-specific test.
13. To support safety of the specification limit of NMT (b) (4) % for impurity (b) (4), provide levels of impurity (b) (4) in the historical marketed Pitressin batches, and/or in the other marketed vasopressin products.
14. Include individual specified identified impurities (b) (4), (b) (4) and (b) (4) (b) (4) with individual shelf-life limits of NMT (b) (4) % in the drug product specifications.
15. The specification limit of NMT (b) (4) % (b) (4) % for individual unidentified impurities of synthetic peptide is not acceptable. All impurities with level of > (b) (4) % should be identified. Therefore, set the limit for individual unidentified impurities as NMT (b) (4) %.
16. Provide results of linearity and accuracy evaluation for all known vasopressin degradation products in the validation of analytical method 20545.
17. We noted that you included testing in upright or inverted vials positions in the stability protocols for long-term, accelerated and intermediate testing of drug product. Revise the stability protocols to clarify that testing in inverted vials positions will be performed or provide comparative data showing that upright and inverted samples have comparative stability.
18. Provide SAS data of all available stability data for supportive Pitressin batches and for primary stability batches used in the stability analysis in the format below. Please provide the above SAS files for marketed Pitressin batches and for primary stability batches separately.

Test	Storage Temperature	Storage RH	Unit	Package	Lot Number	Time (in Month)	Sample Replicate Number	Result
Vasopressin Assay								
...								

PH								
...								

19. Provide a time frame when results of In-use testing for aged multi-dose vials that were stored for the maximal current storage time, will be submitted.
20. Since stability data under accelerated storage conditions showed significant changes, include stability testing for the first three validation lots (manufactured without an overage) at the intermediate conditions in the post-approval stability commitment. Provide post approval stability protocols for testing at intermediate conditions, if different from the stability studies protocol.
21. For your claim of Categorical Exclusion, provide additional statement that, “to the best of JHP Pharmaceuticals LLC knowledge, no extraordinary circumstances exist”.

Labeling: Vials and Container Labels

22. Revise the statement on the carton label “ [REDACTED] (b) (4) ” to “Contains 0.5% chlorobutanol as a preservative”.
23. Revise the dosage potency to “20 USP Vasopressin Units per ml”.
24. Revise the prominence of Pitressin® in the vial and carton labels; it should be commensurate with that of “Vasopressin Injection, USP”.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MARTHA R HEIMANN

03/07/2013

For Ramesh Sood



NDA 204485

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

JHP Pharmaceuticals, LLC
Morris Corporate Centre 2
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

ATTENTION: Gerald Vasquez
Manager, Regulatory Affairs

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vasopressin Injection, USP, 20 USP Vasopressin Units per mL.

We also refer to your December 5, 2012, correspondence, received December 6, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

In addition to the phonetic similarity of this name pair, (b) (4) have overlapping product characteristics including numerical similarity in dose (e.g., 0.1 unit/min vs. 0.001

¹ ISMP's List of High-Alert Medications can be found on ISMP website at www.ismp.org/Tools/highAlertMedications.asp.

unit/min, and 0.05 unit/min vs. 0.0005 unit/min or 0.5 milliunit/min), dosage form (both products are available as solutions for injection), route of administration (intravenous infusion), and rate of administration (both products are prescribed as units/minute and individualized based upon response from the patient). Although the product strengths differ, both products are available in a single strength that has been omitted on prescriptions, demonstrating that strength is not required for filling a prescription, and thus, has not prevented errors from occurring with these products.

We recognize the proprietary name [REDACTED] (b) (4)

First we considered whether labeling or packaging interventions may be sufficient to mitigate the risk of wrong drug errors between [REDACTED] (b) (4). We recognize that the risk of wrong drug medication error due to name confusion may have been increased due to the two products also having similar labeling or packaging, especially if the two products were stored in close proximity to each other. However, we determined labeling and packaging interventions will have minimal impact on minimizing confusion with this name pair. Review of the postmarketing medication errors involving [REDACTED] (b) (4) revealed the confusion occurred during the prescribing, transmission/transcribing, or pharmacy profiling phases of the medication use system where label and packaging interventions are unlikely to prevent these failures.

Secondly we considered whether changing the proprietary name at this time is likely to impact the occurrence of medication errors due to name confusion between [REDACTED] (b) (4) given [REDACTED] (b) (4). We also considered whether some prescribers may [REDACTED] (b) (4)

[REDACTED] (b) (4)

We believe there is an incremental measure of safety that can be gained from the use of a name [REDACTED] (b) (4). Therefore, [REDACTED] (b) (4), given the totality of the factors considered above, we conclude that the name is unacceptable per 21 CFR 201.10(c)(5), which states that labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or

pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Quynh Nguyen at (301) 796-0510.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
03/06/2013

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Transmitted via email to: Steve.Richardson@JHPPHARMA.COM

Attention: Mr. Steve Richardson

Sponsor: JHP Pharmaceuticals, LLC

Phone: (973) 658-3561

Subject: Type C Guidance Teleconference Minutes

Date: February 11, 2013

Pages including this sheet: 5

From: Quynh Nguyen, Pharm.D., RAC
Phone: 301-796-0510
Fax: 301-796-9838
E-mail: quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

Minutes of a Teleconference

Drug: Pitressin (vasopressin) Injection, 1 ml vial (20 pressor units)
NDA: 204-485
Sponsor: JHP Pharmaceuticals, LLC

Date: January 31, 2013
Type: Guidance
Classification: C

FDA Participants:

Peter Hinderling, M.D. Clinical Pharmacologist, Division of Clinical Pharmacology I
Quynh Nguyen, Pharm.D., RAC Regulatory Health Project Manager, Division of Cardiovascular and Renal Products

JHP Pharmaceuticals, LLC Participants:

Steve Richardson (b) (4) Vice President, Scientific & Regulatory Affairs
Clinical Consultant
Clinical Consultant
Clinical Consultant
Gerald Vasquez Manager, Regulatory Affairs

Background

JHP Pharmaceuticals, LLC submitted a 505(b)(2) NDA for Pitressin (vasopressin) Injection on September 26, 2012. Pitressin is currently a marketed, unapproved product. The NDA is based on the published literature. On January 29, 2013, a clinical pharmacology Information Request (IR) was emailed to the sponsor (see attached). As part of their response, the sponsor requested additional clarification on the IR. A brief teleconference was subsequently scheduled on January 31, 2013 to clarify the IR.

Teleconference

Dr. Hinderling explained that several of the clinical and clinical pharmacology articles on arginine vasopressin published between 1980 and 2010 used the Ferring product. Most of these articles provided information on the dosage strength in terms of U/min. Only the article by Moehring et al. 1980 (J Cardiovasc Pharm 1980;2:367-376) provided information on pressor units and weight units. Based on the Moehring article there is a 40-50% difference in the potency between the Ferring product and the sponsor's product. In order to relate exposure and response, information on pressor and weight units should be available for all publications that used the Ferring product. The potency of the Ferring product may have changed between 1980 and 2010. Therefore, this information is important. The sponsor indicated that it will be difficult to get this information, because some of the publications were old and Ferring is domiciled in Sweden. The sponsor also pointed out that some of the above articles were not in their submission. Dr. Hinderling pointed out that his review identified a number of relevant publications that were not included in JHP's submission. The sponsor agreed to make a best effort to get the requested information in the shortest time interval possible.

Conclusion

This teleconference was scheduled to clarify the clinical pharmacology IR with regards to verifying the potency of Ferring's arginine vasopressin product that was used in the clinical trials cited in the published literature.

Recorder: *{See appended electronic signature page}*
Quynh Nguyen, Pharm.D., RAC

Chair Concurrence: *{See appended electronic signature page}*
Peter Hinderling, M.D.

RD:
P Hinderling 2-3-13

From: [Vasquez, Gerald](#)
To: [Nguyen, Quynh M](#)
Subject: RE: NDA 204-485/Pitressin - Clinical Pharmacology IR
Date: Wednesday, January 30, 2013 3:05:53 PM

Dear Quynh,

Thanks for your follow up voicemail.

We discussed your information request yesterday within JHP and a few clarification questions came to mind:

- Is the review group concerned about hypotension?
- Could you help us understand the concerns related to the conversion factors?

Given that the article referenced below is approximately 32 years old and it was not cited as part of our submission, we are trying to learn more about the questions asked. Also, we wanted to share with you that the product referenced in the article was manufactured by Ferring Pharma in Malmo, Sweden and as such, we believe it will be very difficult to address the information requested below. Certainly, we will not be able to provide this information by February 8.

However, we are hoping that with a bit more clarification from the reviewers we can get a better understanding of the information requested and be able to provide more detailed information pertinent to our NDA filing.

I look forward to your response.

Thank you,

Gerald

From: Nguyen, Quynh M [mailto:Quynh.Nguyen@fda.hhs.gov]
Sent: Tuesday, January 29, 2013 3:14 PM
To: Vasquez, Gerald
Subject: NDA 204-485/Pitressin - Clinical Pharmacology IR

Dear Mr. Vasquez,

It was good speaking with you earlier today. Regarding NDA 204-485/Pitressin, per our telephone conversation this afternoon, please find below the following Clinical Pharmacology Information Request:

Please provide information on the respective factors to convert pg or pmol to mU for the synthetic arginine-vasopressin manufactured by Ferring, that was used by published clinical pharmacology and clinical trials performed between 1980 and 2010. The publication of Moehring et al 1980 J Cardiovasc Pharm 1980;2:367-376 ("Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic, orthostatic hypotension") states on p. 369 that "1 pmole is equivalent to approximately 0.4 mU". Please verify with Ferring the accuracy of that statement.

Please provide this information as soon as possible, but not later than by February 8.

Also, thank you for your update on the status of the response to the 12-7-12 Filing Communication Letter and for letting me know that you are still working on a response. As I mentioned, you do not need to submit all the responses in one submission, so you may submit whatever information you have complete by piecemeal and we will review the responses as they come in. Thanks again and please let me know if you have any questions.

Thanks,
Quynh

Quynh M. Nguyen, Pharm.D., RAC
CDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/ODE1/DCRP
Tel: (301) 796-0510
Fax: (301) 796-9838
quynh.nguyen@fda.hhs.gov

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/s/

PETER HINDERLING
02/11/2013



NDA 204485

FILING COMMUNICATION

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pitressin (vasopressin) Injection, 1 ml vial (20 pressor units).

We also refer to your amendment dated November 29, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 26, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 26, 2013.

We request that you submit the following information:

Product Quality

1. Provide the batch size of the Pitressin® Injection registration batches, and batch size for batches used in the supportive stability studies. Indicate whether these batches are of commercial or pilot scale.
2. Provide additional drug product stability data for primary stability batches (beyond the 2-3 months data) by the mid-cycle timeframe, February 26, 2013, in order to receive the reasonable expiration dating period.

3. You have provided the in-use stability data for multi-dose Pitressin® Injection drug product after initial withdrawal of drug from multiple dose vials. Provide the in-use stability data, including test results for assay, impurities and antimicrobial effectiveness, after multiple periodic withdrawals. In addition, include in-use testing for aged multi-dose vials that were stored for the maximal current storage time.
4. State in the labeling (container labels and package insert) the maximum storage time period of Pitressin® in vials after initial withdrawal of drug.
5. Provide a Method Validation Package for drug substance and drug product Pitressin® Injection in the Section R3 of the Regional Information (R).

Please provide the above information as soon as possible.

Microbiology

1. Your application does not contain microbiological data to support an extended post-dilution hold period. Without this data, drug product labeling should recommend that the post-dilution storage period is not more than 4 hours at room temperature or 24 hours under refrigeration. If you desire a longer hold period, microbiological data should be provided to demonstrate that the diluted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E* and *Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7*. Generally, "no growth" is interpreted as not more than a 0.5 log₁₀ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3 times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (<100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.
2. The drug product specifications that you provided state an endotoxin acceptance criterion of NMT ^{(b) (4)} EU/ml drug product, but the drug product testing methods (3.2.P.5.2) state an acceptance criterion of ≤ ^{(b) (4)} EU/ml. Please clarify.
3. For annual requalification of the ^{(b) (4)} ^{(b) (4)}, describe biological indicators used, including ^{(b) (4)} and handling methods. State acceptance criteria for these requalification studies.
4. For annual requalification of the ^{(b) (4)} ^{(b) (4)}, describe ^{(b) (4)} used, including ^{(b) (4)} and handling methods. State acceptance criteria for these requalification studies.
5. For annual requalification studies of the sterilization ^{(b) (4)} and handling methods. State acceptance criteria for these requalification studies.

Please provide the above information as soon as possible.

Clinical Pharmacology (These comments were previously conveyed via email on November 29, 2012.)

A first review of the 77 publications submitted in the NDA and the 15 publications that support labeling shows that:

1. A number of publications potentially providing useful information on exposure and exposure-response to vasopressin and impacting co-factors were not included in the submission and examples are listed below:

- Moses et al J Clin Endocrinol 1990; 70: 222-229
- Davison et al Am J Physiol 1993; 264:F348-F353
- Hensen et al J Endocrinol Metab 1988;66:668-671
- Erfurth et al. Horm Metab Res 1996;28;599-602
- Stachenfeld et al. J Physiol 2003; 552:869-880
- Moehring et al J Cardiovasc Pharmacol 1980;2:367-376

We recommend that you indicate the criteria you applied in selecting the 77 publications submitted in the NDA and the 15 publications that support labeling. You should provide a list detailing the individual criteria you applied to ascertain that methods and results reported by the publications you selected are accurate. From the listed criteria it should also follow why you did not consider the other available publications.

2. Source and identity of the vasopressins used are not indicated in all the publications you submitted. We ask you to provide complete information on the drug product, drug substance, MW, biopotency and correction factors to be used for calculating mass units from pressor units and vice versa for all vasopressins used in the relevant publications. This information is not only necessary to calculate parameters such as clearance and volume of distribution or to check the accuracy of published parameters for the individual AVPs, but also to compare the results obtained with different AVPs. To this end it may be necessary to contact the authors of the relevant publications and/or the manufacturers of the different vasopressins used. The products used in the publications that identified product and manufacturer included: Pitressin (extract from the posterior pituitary containing AVP and LVP), synthetic Pitressin®, Argipressin® (Parke-Davis), AVP (Ferring), and AVP (Schwarz/Mann).

Please provide the above information as soon as possible, but not later than December 13, 2012.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling issues:

Format Comments

Highlights (HL)

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: Correct the margins to be ½ inch on all sides. We recommend that you use 8-point to meet the ½ page length requirement for the Highlights.
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).

Comment: Correct the length of HL to be less than or equal to one-half page. A waiver request of the one-half page requirement has not been submitted.

3. 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)" and not "(1.2)" as proposed. Additionally, the statement "Pitressin® is incompatible with 5% dextrose (D5W) and this diluent should NOT be used to dilute Pitressin®." should have an identifier "(2)."

4. 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: Correct the HL Limitation Statement to be located on the line immediately beneath the HL heading. The proprietary name should be in UPPER CASE in both sentences.

5. 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: Correct the placement of the initial U.S. Approval in HL so that it is immediately beneath the product title.

6. In CONTRAINDICATIONS, each contraindication is bulleted when there is more than one contraindication.

Comment: There is more than one contraindication and each contraindication should be bulleted.

Contents: Table of Contents (TOC)

7. 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. Please correct.

Full Prescribing Information (FPI)

8. The following heading must appear at the beginning of the FPI in UPPER CASE and bolded: "FULL PRESCRIBING INFORMATION".

Comment: You have italicized this heading and it should be un-italicized.

9. In ADVERSE REACTIONS, 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: You should re-title Section 6.1 to "Clinical Trials Experience." You 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.

10. In ADVERSE REACTIONS, 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: You should re-title Section 6.2 to "Postmarketing Experience." You should include the relevant limitation statement in this section. Section 6.2 includes adverse reactions from voluntary, spontaneous reports (from AERS).

Additional Non-Format Comments

Dosage and Administration

1. You propose a maximum dosage for septic shock, but do not propose a maximum dosage for post-cardiotomy shock. If you believe there should be a maximum dosage for post-cardiotomy shock in adults or pediatric patients include this maximum dosage in the prescribing information.
2. You propose a dosage for "children" with post-cardiotomy shock; however, you do not specify the pediatric age groups. Specify the pediatric age groups.
3. In Section 2.3, you propose dosage modifications; however, it is not clear whether this applies to children. Specify if this dosage modification applies to children.

Warnings and Precautions

4. Your proposed Warnings and Precautions section is not consistent with the Warnings and Precautions regulations [see 21 CFR 201.57(c)(6)] and the 2011 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance* (see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>) because it does not include the following about clinically significant adverse reactions (ARs): a description, known risk factors, outcome, risk mitigation strategies to reduce the risk of the clinically significant ARs, and steps to take if the clinically significant ARs occur (all of these items may not be applicable). Furthermore, several clinically significant ARs included in your proposed Adverse Reaction section should be Warnings and Precautions. Consider including several of these ARs in the Warnings and Precautions section. Finally, include subsections for each distinct clinically significant AR in the Warnings and Precautions section (each subsection title should be an adverse reaction).

Adverse Reactions

5. Your proposed Adverse Reactions section is not consistent with the 2006 *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance*. See the guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>

Drug Interactions

6. Your proposed Drug Interactions section is not consistent with the 2012 *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* Guidance. See the guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. The Drug Interactions section should include risk mitigation strategies for clinically significant drug interactions and include mechanisms of the drug interactions (if known).

References

7. You propose many references. However, only references should be included if they are from an authoritative scientific body, standardized methodology, scale, technique, or similar material important to prescribing decisions that are mentioned in another section of labeling, but cannot readily be summarized. Remove unnecessary references.

Patient Counseling Information

8. Include important information the prescriber should tell the family members about Pitressin.

We request that you resubmit labeling that addresses these issues by January 7, 2013. The resubmitted labeling will be used for further labeling discussions.

Administrative

1. Provide a detailed regulatory history for Pitressin that includes the dates of submission, approval, and withdrawal of previous NDAs for this product, previously approved indications, formulations, strengths, etc., and currently marketed formulations, strengths, etc.
2. Your request for a full waiver of pediatric studies did not contain a complete certification statement. Please resubmit a certification statement that contains language stating that you certify that all statements made in your pediatric waiver request are true and correct, and that the information is believed to adequately support your request for a full waiver of pediatric studies. The certification statement should be followed by your signature, name, title, and date.

Please provide the above information as soon as possible.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
11/27/2012



NDA 204485

NDA ACKNOWLEDGMENT

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Manager, Regulatory Affairs
Morris Corporate Center 2
One Upper Pond Rd., Bldg. D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Pitressin (vasopressin) Injection

Date of Application: September 25, 2012

Date of Receipt: September 26, 2012

Our Reference Number: NDA 204485

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
10/05/2012



PIND 112944

MEETING MINUTES

JHP Pharmaceuticals
Attention: Gerald Vasquez
Manager, Regulatory Affairs
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Pitressin (vasopressin injection, USP) for the treatment of vasodilatory shock.

We also refer to the telecon between representatives of your firm and the FDA on October 17, 2011. The purpose of the meeting was to discuss your development program for vasopressin.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Michael Monteleone at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND

Meeting Date and Time: October 17, 2011 4PM EST
Meeting Location: Telecon

Application Number: PIND 112944
Product Name: Pitressin (vasopressin injection, USP)
Indication: Vasodilatory shock
Sponsor/Applicant Name: JHP Pharmaceuticals

Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Michael Monteleone, MS

FDA ATTENDEES

Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Shari Targum, MD	Clinical Team Leader
Monica Fiszman, MD, PhD	Clinical Reviewer
Thomas Papoian, PhD	Pharmacology/Toxicology Team Leader
Rama Dwivedi, PhD	Pharmacology/Toxicology Reviewer
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Michael Monteleone, MS	Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Jennifer Johnson	Regulatory Project Manager
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SPONSOR ATTENDEES

JHP Pharmaceuticals, LLC

Steve Richardson	VP, Scientific and Regulatory Affairs
Marty Joyce	VP, Product Development
Mike Bergren	Director, Chemistry and Analytical Development
Gerald Vasquez	Manager Regulatory Affairs
	Regulatory Consultant

(b) (4)

Consultant

(b) (4)

Consultant

(b) (4)

Consultant

1.0 BACKGROUND

The Sponsor, JHP Pharmaceuticals, LLC is seeking advice on their strategy to pursue a 505(b)(2) New Drug Application (NDA) for Pitressin (vasopressin injection, USP). Pitressin is an unapproved, marketed product. (b) (4)

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A teleconference was held between the sponsor and DCRP on November 17, 2011, the minutes of that discussion follow.

2.0 PRELIMINARY RESPONSE

Prior to the teleconference, DCRP provided the sponsor with the following preliminary comments to their questions as they relate to the vasodilatory shock indication;

Question 1:

Pitressin® (vasopressin) has a well-documented use based on literature and standard usage manuals (such as the American Hospital Formulary Service (AHFS) Manual, 2011). Because of this documented usage, JHP believes the following clinical indications can be supported by the available literature and usage manuals and should be included in the Package Insert.

Pitressin® is an antidiuretic hormone indicated for the treatment of:

- *Vasodilatory shock**

**indication not on current Pitressin® label*

Does FDA agree this is acceptable?

DCRP Preliminary Response:

We believe it may be possible to approve vasopressin without further outcome studies for increasing systemic arterial blood pressure in certain acute hypotensive states. We believe that increasing blood pressure in shock with vasopressin can be interpreted to be desirable and so may serve as a basis for approval. Vasopressin's hemodynamic effect would need to be sufficiently understood (from literature or prospective studies of pharmacodynamics) to write instructions for use (dosing regimens, time course of effects).

If you submit a NDA, we expect you to submit any information to which you have access concerning the safety and efficacy of vasopressin for this indication. That information should include a thorough review of clinical studies in the literature

relevant to the effects of vasopressin in the treatment of vasodilatory shock. A single unblinded trial (Dünser et. al.) with no single prespecified primary efficacy variable and no measures to control bias is not sufficient to support a NDA. We are aware of many other published reports of studies of the administration of vasopressin for vasodilatory shock. Please also be aware that expert opinions, consensus documents or guidelines are not considered evidence of effectiveness.

Question 2:

For the clinical sections of the NDA JHP will provide summaries of published references to confirm safety and efficacy of vasopressin within Module 2. Copies of the cited references will be provided in Module 5. No clinical studies will be conducted by the Sponsor.

Does FDA agree this is acceptable?

DCRP Preliminary Response:

Please refer to our answer for question 1.

Question 3:

Because of the long, published history of clinical use, JHP intends to update the Package Insert with information to support the Indications, Dosing schedules (adult and pediatric), and Safety using Pitressin® postmarketing data, well-established publications, and standard usage manual such as the AHFS manual. A draft Package Insert will be provided in the Information Package. JHP believes this is an appropriate manner in order to provide the most updated information to the prescribers.

Does the FDA find this acceptable?

DCRP Preliminary Response:

We note that the draft label you provide in the materials for this meeting includes

(b) (4) indications, the (b) (4) for which you have submitted questions, (b) (4) (b) (4) vasodilatory shock, (b) (4)

We do not believe that literature alone can support the use of vasopressin in the (b) (4) but rather a clinical outcome study would be required for support.

3.0 DISCUSSION DURING THE MEETING

Prior to the tcon, the sponsor indicated that they would like to discuss any non-clinical data that might be required specifically for a vasodilatory shock indication.

The sponsor began the discussion with a brief description of the setting in which vasopressin might be used for vasodilatory shock, particularly that it would be intended for short term use in patients who were being closely monitored. The sponsor commented that no additional nonclinical studies were planned, and that literature was adequate to identify target organ effects. Further, the sponsor commented that another goal of non-clinical studies might be to determine the therapeutic index, which the sponsor contends may not be relevant given vasopressin is dosed to effect. The sponsor also offered that they intend to conduct a thorough review of the literature for any adverse reactions of vasopressin.

Dr. Papoian commented that DMEP had requested the sponsor conduct a one-month bridging non-clinical safety study and that DCRP concurred. Dr. Papoian asked the sponsor if the proposed product was already in wide clinical use. The sponsor responded that their specific product goes back 20-30 years. Dr. Papoian commented that the current formulation should be considered qualified for safety after that much clinical experience, and that he would not ask for additional animal studies if additional toxicity concerns can be satisfied from the literature. In particular, Dr. Papoian stated that he did not think carcinogenicity would be an issue, given the short term use. QT effects and reproductive toxicity could be an issue, even in short term use, but these concerns might be satisfied from the literature.

Dr. Papoian asked the sponsor to describe the previously mentioned high level of impurities in the product, and whether these were process impurities or peptide degradants. The sponsor responded that impurities could be as high as (b) (4)%, (b) (4)

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The sponsor asked the Division to comment on the utility of a PK study to evaluate differences from the start of shelf life versus the end. Dr. Grant commented that such a study might be useful to write adequate instructions in the label for use by physicians. Dr. Stockbridge commented that if the study showed a significant decline over time, the Division might approve with a shorter shelf life. Dr. Targum elaborated on what might be needed to write adequate instructions for use, saying that it is important to know at what dose to start, when to up-titrate, how much to up-titrate, as well as when additional up-titration would prove futile. The sponsor commented that this might be found in the literature. Dr. Grant cautioned that may be true, but the sponsor should be aware that guidance and consensus documents alone would not be adequate and that the information provided thus far by the sponsor is not sufficient.

The sponsor commented that they would evaluate their discussions with DCRP and DMEP, but that they are generally looking at the second quarter of 2012 for an NDA submission.

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/s/

NORMAN L STOCKBRIDGE
10/24/2011