CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204485Orig1s004

Trade Name:	VASOSTRICT
Generic or Proper Name:	Vasopressin injection
Sponsor:	PAR Sterile Products LLC
Approval Date:	12/21/2016

Indication:

Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines

CENTER FOR DRUG EVALUATION AND RESEARCH

204485Orig1s004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204485/S-004

APPROVAL LETTER

Par Sterile Products, LLC
Attention: Carla English, Senior Manager Regulatory Affairs
One Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated March 18, 2016, received March 18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict® (vasopressin injection, USP).

We acknowledge receipt of your amendment dated April 1, 2016, August 17, 2016, November 18, 2016, and December 9, 2016.

The August 17, 2016 amendment constituted a complete response to our July 18, 2016, action letter.

This "Prior Approval" supplemental new drug application provides for the addition of a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on August 17, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204485/S-004.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

Ramesh Raghavachari -S

Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2016.12.17 09:22:09 -05'00'

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204485/S-004

COMPLETE RESPONSE

Par Sterile Products, LLC
Attention: Carla English, Senior Manager Regulatory Affairs
One Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated March 18, 2016, received March 18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict® (vasopressin injection, USP).

We acknowledge receipt of your amendment dated April 1, 2016.

This "Prior Approval" supplemental new drug application provides for the addition of a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Provide additional stability data to support the proposed expiration period for 10 mL multiple dose presentation.

LABELING

A. General Recommendations (vial container label and carton labeling)
   1. Revise the product strength for the 10 mL multiple-dose vial as the total quantity per total volume followed by the concentration per milliliter, such that it reads 200 units per 10 mL (20 units per mL).
   2. Revise the 10 mL container labels and carton labeling so that they use a (b) (4) (b) (4) between the currently marketed Vasostrict 20 units/mL product and the proposed Vasostrict 200 units/10 mL product, in order to prevent strength confusion and selection errors. In addition, consider other features that may further differentiate the container labels and carton labeling of the two different strengths of Vasostrict products.

3. We note that the PI states "Do not freeze," but the container label and carton labeling do not contain this warning. If space allows, include the warning, "Avoid freezing," on the container label and carton labeling.
4. The container label and carton labeling recommend to [redacted] (b) (4) [redacted] (b) (4)" Specify what storage condition applies (e.g., refrigeration or at room temperature) to the 30 days after first puncture.

B. Container Label
1. If space allows, we recommend removing the phrase, "[redacted] (b) (4) and adding in its place the following storage information: "Vials may be held at 20 °C to 25 °C (68 °F to 77 °F) for up to 12 months."

C. Carton Labeling
1. Ensure the lot number and expiration date are present on the carton labeling. Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.
2. Consider relocating the following statement, "Do not store above 25 °C (77 °F)." to after the statement discussing storage between 20 °C to 25 °C, as follows: "Vials may be held at 20 °C to 25 °C (68 °F to 77 °F) for up to 12 months. Do not store above 25°C (77 °F)." This reorganization provides the appropriate action first in relation to storage at room temperature, instead of what not to do (negative statement) first.

Your response must include 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.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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 with the supplement number for previously-approved labeling changes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Ramesh Raghavachari

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Date: 7/18/2016 03:22:37PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

LABELING

Vasostrict®
(vasopressin injection, USP)
For Intravenous Infusion

3003619D

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VASOSTRICT® safely and effectively. See full prescribing information for VASOSTRICT®.

VASOSTRICT® (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

- Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dilute Vasostrict® with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 20 units per mL (3)

----------CONTRAINDICATIONS----------

- Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

----------WARNINGS AND PRECAUTIONS----------

- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Pressor effects of catecholamines and Vasostrict® are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict®. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

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

- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict®	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial.

4 CONTRAINDICATIONS

Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict® on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict® on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict® on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide,

felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict®.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict® in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict® may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.

Vasostrict® may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict® in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

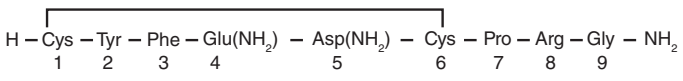
Overdosage with Vasostrict® can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP, and sodium acetate buffer adjusted to a pH of 3.8. The 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)]*.

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)]*.

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)]*.

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Special Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as:

NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.

NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL).

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial.

After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrigerated 10 mL vial after 30 days after first puncture.

The storage conditions and expiration periods are summarized in the following table.

	Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F) Do not store above 25°C (77°F)	Opened (After First Puncture)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A
10 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R12/16 OS164J-01-90-08

NDC 42023-**190**-01 Rx Only

Vasostrict®

(Vasopressin Injection, USP)

200 Units per 10 mL
(20 Units per mL)

For Intravenous Infusion
Must be diluted prior to use
Store between 2°C and 8°C (36°F and 46°F).
Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months. Avoid freezing.

10 mL Multiple Dose Vial

Dosage: See full prescribing information. After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

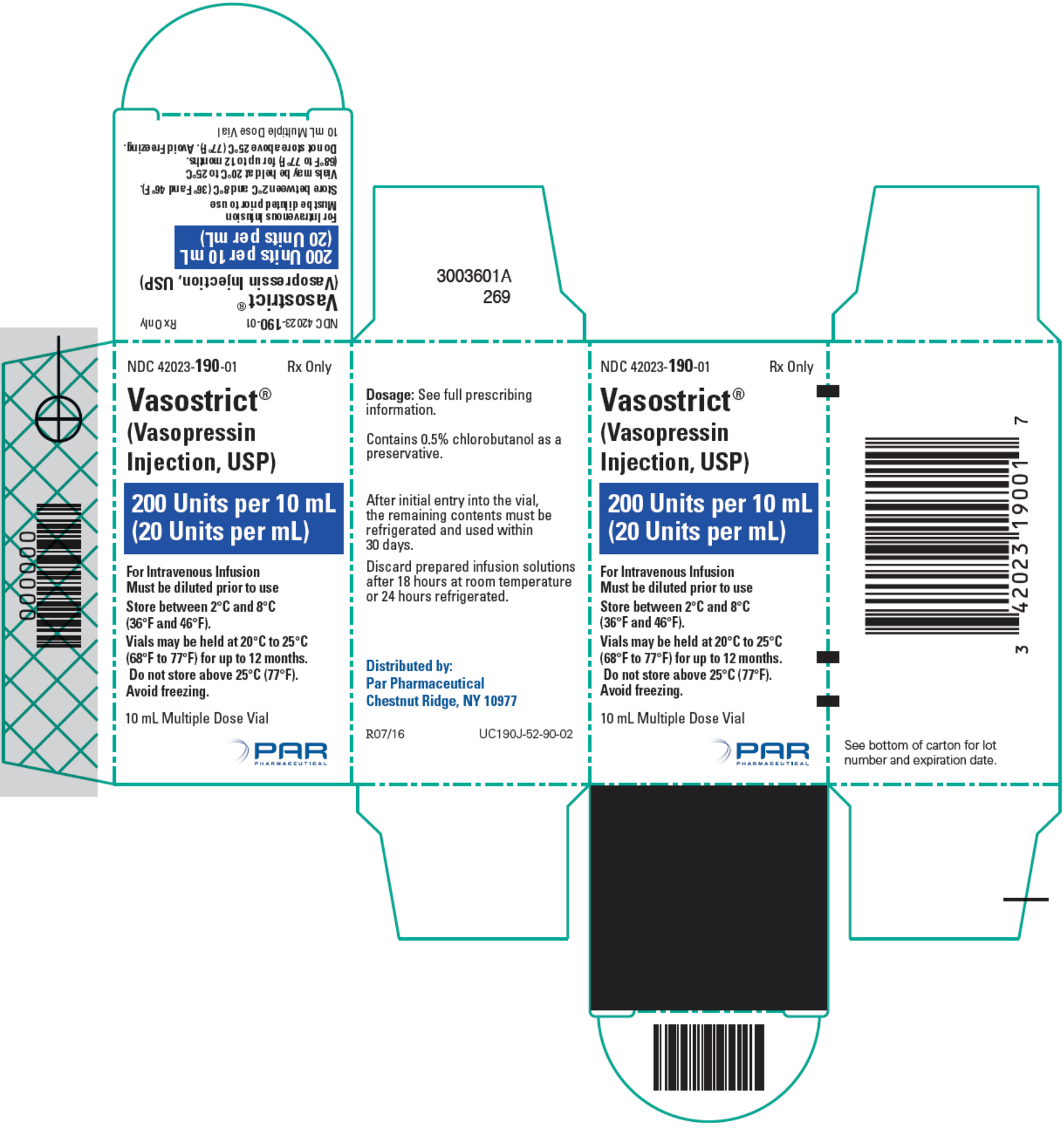
R07/16 LA190J-52-90-02

(01)00342023190017

3 0 0 3 6 0 2 A

LOT

EXP



NDC 42023-190-01 Rx Only

Vasostrict®
(Vasopressin Injection, USP)

200 Units per 10 mL
(20 Units per mL)

For Intravenous Infusion
Must be diluted prior to use
Store between 2°C and 8°C
(36°F and 46°F).
Vials may be held at 20°C to 25°C
(68°F to 77°F) for up to 12 months.
Do not store above 25°C (77°F).
Avoid freezing.

10 mL Multiple Dose Vial

PAR PHARMACEUTICAL

3003601A
269

Dosage: See full prescribing information.

Contains 0.5% chlorobutanol as a preservative.

After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days.

Discard prepared infusion solutions after 18 hours at room temperature or 24 hours refrigerated.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R07/16 UC190J-52-90-02

NDC 42023-190-01 Rx Only

Vasostrict®
(Vasopressin Injection, USP)

200 Units per 10 mL
(20 Units per mL)

For Intravenous Infusion
Must be diluted prior to use
Store between 2°C and 8°C
(36°F and 46°F).
Vials may be held at 20°C to 25°C
(68°F to 77°F) for up to 12 months.
Do not store above 25°C (77°F).
Avoid freezing.

10 mL Multiple Dose Vial

PAR PHARMACEUTICAL

3 42023 19001 7

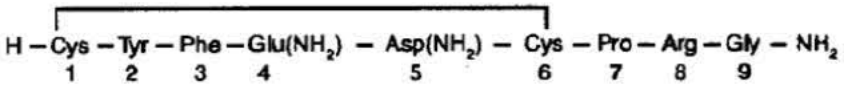
See bottom of carton for lot number and expiration date.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW: 2	1. ORGANIZATION:	2. NDA Number: 204-485
3. Name and Address of Applicant (City & State): Par Sterile Products 1 Ram Ridge Road Chestnut Ridge, New York 10977		**4. Supplement(s):** **Number(s)** **Date(s)** S-004 3/18/2016
5. Drug Name: Vasostrict®	**6. Nonproprietary Name:** Vasopressin	**7. Amendments: - Dates** S-004 (RESUB) 8/17/2016 S-004 (RESUB) 12/9/2016
8. Supplement Provides For: approval of a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product.		
1. Pharmacological Category: To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.	**10. How Dispensed:** Rx	**11. Related NDAs:**
12. Dosage Form(s): Injection	**13. Potency:** 20 units/mL	
14. Chemical Name and Structure: Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide.  Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular weight: 1084.23 One mg is equivalent to 530 units		**15. Records/Reports:** **Current** **Yes X** **No** **Reviewed** **Yes** **No X**

16. Comments: Par submitting this **PA** supplement seeking approval of a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product. During the first review cycle OSE recommended changes in the labeling. Additionally, stability data was needed to support the proposed expiration period of 24 months for 10 mL multiple dose presentation. A CR letter was sent to the applicant on July 18, 2016 to provide response to the OSE comments on labeling along with the required additional stability data to support the proposed 24-month expiration for the drug product. On 8/17/2016 the applicant provided the responses to the Agency's questions. Pertinent CMC information was reviewed by this reviewer (Kris Raman, Ph.D.) and found acceptable to support the proposed 24-month expiration for the drug product.

After evaluation of the revised **container label** and **carton labeling** (*amendment dated, 8/17/2016*) and the revised **Package Insert** (*amendment dated, 12/9/2016*), DMEPA (Sarah Thomas, PharmD) concluded that PAR Sterile Products LLC incorporated their recommendations and found the revised **container and carton labeling** and **Package Insert** for Vasostrict (Vasopressin) Injection are acceptable from a medication error perspective.

17. Conclusions and Recommendations: This supplement is approved.

18. Reviewer:

Name: Kris Raman, Ph.D. Sr. CMC Reviewer	**Signature:**	**Date Completed:** 11/8/2016, 12/15/2016

CMC REVIEW NOTES

DRUG PRODUCT STABILITY:

Results were evaluated from 12 registration stability studies up to 9 months at 5°C and up to 6 months at 25°C/60%RH in both upright and inverted orientations for the registration batches (**RC3300, RC3301,** and **RC3302**) of Vasostrict® 10 mL.

A detailed analysis of the registration stability studies is provided in section 3.2.P.8.3.

Summary of Stability Batches:

Table 1: Summary of Stability Batches

Study	Lot	Condition		Orientation	Study Duration
		°C	%RH		
QCP01896.05I	RC3300	05	Not Defined	Inverted	24 Months
QCP01896.05U	RC3300	05	Not Defined	Upright	24 Months
QCP01896.25I	RC3300	25	60	Inverted	6 Months
QCP01896.25U	RC3300	25	60	Upright	6 Months
QCP01897.05I	RC3301	05	Not Defined	Inverted	24 Months
QCP01897.05U	RC3301	05	Not Defined	Upright	24 Months
QCP01897.25I	RC3301	25	60	Inverted	6 Months
QCP01897.25U	RC3301	25	60	Upright	6 Months
QCP01898.05I	RC3302	05	Not Defined	Inverted	24 Months
QCP01898.05U	RC3302	05	Not Defined	Upright	24 Months
QCP01898.25I	RC3302	25	60	Inverted	6 Months
QCP01898.25U	RC3302	25	60	Upright	6 Months

(b) (4)

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(b) (4)

Evaluation:

An analysis of the stability data for the 10 mL presentation was performed. Under accelerated conditions (25°C/60%RH), vasopressin assay, (b) (4) and total impurities showed slight increase but still well below the acceptance criteria. However, according to the applicant, after 3 months these trends were consistent or better when compared to the current approved 1 mL presentation. All other attributes, such as, description, microbiological, known and unknown impurities showed no significant change or observable trend under accelerated conditions. The results under long term conditions (5°C) did not show any significant trend over the 3 month period.

Expiration Period:

The currently approved 1 mL presentation has a shelf-life of 24 months at 2°C - 8°C with a time out of refrigeration period of up to 12 months at USP controlled room temperature during the 24 months shelf-life of the product. Results from the 10 mL stability studies, when compared to the approved 1 mL stability data, were consistent and expected to remain within specification for the same storage conditions.

Additional available stability data supports Par's proposed *expiration date of 24 months* at 2°C - 8°C with a time out of refrigeration period of up to 12 months at USP controlled room temperature during the 24 months shelf-life of the product for the 10 mL presentation.

LABELING:

The following are the revised labeling submitted on 8/17/2016 (**amendment**) per OSE/DMEPA'S (Sarah Thomas, PharmD) recommendations.

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(b) (4)

[redacted]

OSE/DMEPA Comments:

After evaluation of the revised container label and carton labeling, DMEPA concludes that PAR Sterile Products considered their recommendations and implemented most of the recommended changes. DMEPA found the revised **container label** and **carton labeling** for Vasostrict (vasopressin) injection (in amendment of 8/17/2016) **acceptable** from a medication error perspective. However, DMEPA noted that the recommendations for the **PI** from DMEPA's previous review were not implemented. Therefore, DMEP again recommended the same recommendations made in their previous review, prior to approval of this NDA supplement.

An IR was sent to the applicant on 11/9/2016 (by Yvonne Knight) to address DMEPA's recommendation with respect to **PI**.

The applicant amended the supplement on 12/09/2016 per DMEPA's recommendations on **PI**. The revised **PI** was found acceptable to DMEPA.

The following CMC deficiencies were identified in the submission with respect to the drug product description. An **Information Request** was sent to the applicant to respond.

(1) Revise the product description in **Section 3** and **Section 16** of the **Package Insert** to state, "clear, practically colorless solution".

(b) (4)

[redacted]

Amendment, dated 12/09/2016:

The applicant submitted the following responses to FDA's IR:

Applicant's Response to Q 1:

Revised the product description in Section 3 and Section 16 of the Package Insert to state, "clear, practically colorless solution". See below is the side-by-side comparison.

Revised Package Insert (11/2016) According to FDA Information Request Dated 11/09/2016	Revised Package Insert (12/2016) According to FDA Information Request Dated 12/06/2016
(b) (4)	**3 DOSAGE FORMS AND STRENGTHS** Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. **4 CONTRAINDICATIONS** Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. **5 WARNINGS AND PRECAUTIONS** **5.1 Worsening Cardiac Function** Use in patients with impaired cardiac response may worsen cardiac output.
Updated Section 3, Dosage Forms and Strengths according to FDA IR dated 12/6/2016, comment #1.	

Revised Package Insert (11/2016) According to FDA Information Request Dated 11/09/2016	Revised Package Insert (12/2016) According to FDA Information Request Dated 12/06/2016
(b) (4)	**16 HOW SUPPLIED/STORAGE AND HANDLING** Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as: NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL. NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/mL (20 units/mL). Store between 2°C and 8°C (36°F and 46°F). Do not freeze. Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial. After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrigerated 10 mL vial after 30 days after first puncture. The storage conditions and expiration periods are summarized in the following table.
Updated Section 16, How Supplied/Storage and Handling according to FDA IR dated 12/6/2016, comment #1.	

Comment: ***Acceptable.*** **The applicant has made the recommended changes in the PI per Agency's request.**

Applicant's Response to Q 2:

Revised product description in the approved drug product specification.

Summary of Changes - Product Release Specification

SECTION	CHANGE FROM:	TO:	REASONING/JUSTIFICATION
			(b) (4)

Summary of Changes - Product Shelf Life Specification

SECTION	CHANGE FROM:	TO:	REASONING/JUSTIFICATION
			(b) (4)

Comment: ***Acceptable.*** The applicant has made the recommended changes per Agency's request.

Conclusion:

This supplement is approved.

Krishna P. Raman -S

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Ramesh Raghavachari -S

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

July 6, 2016

NDA: 204485/S-004

Drug Product Name
Proprietary: Vasostrict
Non-proprietary: vasopressin injection, USP

Review Number: # 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
3/18/16	3/18/16	N/A	5/3/16

Submission History (for 2nd Reviews or higher): N/A

Applicant/Sponsor
Name: Par Sterile Products, LLC
Address: One Ram Ridge Road, Chestnut Ridge, NY 10977
Representative: Carla English
Telephone: 845-573-5728
Email: regulatory.psp@parpharm.com

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: PAS

2. SUBMISSION PROVIDES FOR: New 10 mL vial presentation for the drug product.

3. MANUFACTURING SITE:
Par Sterile Products, LLC
870 Parkdale Road,
Rochester, MI 48307

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile injection for intravenous infusion
- 20 units/mL
- 1 mL and 10 mL multiple dose vial

5. METHOD(S) OF STERILIZATION: (b) (4) (b) (4).

6. PHARMACOLOGICAL CATEGORY: Treatment of vasodilatory (post-cardiotomy or septic) shock.

B. SUPPORTING/RELATED DOCUMENTS: Microbiology review N204485R1.doc (5/5/13), for the 1 mL vial presentation of the drug product.

C. REMARKS: An e-CTD submission.

Filename: N204485S004MR01.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - The submission is recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies –None identified.

C. Assessment of Risk Due to Microbiology Deficiencies – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Dupeh Palmer, Ph.D.
Acting Microbiology Quality Assessment Lead - Branch 3/Jessica Cole, Ph.D.

C. CC Block

cc: Panorama review platform

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW #1

Office of Pharmaceutical Quality
Office of Programs and Regulatory Operations

Application Number: NDA 204485/S-004

Name of Drug: Vasostrict® (vasopressin injection, USP)

Applicant: PAR Sterile Products

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Content of Labeling (SPL)	12/9/16	12/9/16	3/18/16 (last approved in S-003
Carton and Container Labels	8/17/16	8/17/16	3/18/16 (last approved in S-003

Background and Summary

This PAS supplement was received on March 18, 2016, and provides for the addition of a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product. DMEPA reviewed the proposed labeling and deficiencies regarding the carton and container labels were sent to the applicant in the July 18, 2016, Complete Response letter. The applicant submitted a resubmission on August 17, 2016. The applicant adequately addressed the carton and container labeling deficiencies; however DMEPA had PI deficiencies that still needed to be addressed (see Sarah Thomas DMEPA review dated October 29, 2016). DMEPA's PI comments were then revised by DCRP Division and then communicated to the applicant on November 9, 2016. The applicant adequately addressed the PI comments (see DEMPA memo dated December 15, 2016). On November 30, 2016, CMC requested a t-con so the applicant can provide clarification regarding drug product specifications description. The applicant amended the drug product specifications description in the PI on December 12, 2016. CMC found the amendment acceptable and recommended approval (See Kris Raman CMC review dated December 16, 2016).

Review

This comparison was done by visually comparing the proposed to the last approved labeling on file.

The following are the assessments for each change identified:

Content of Labeling:

HOW SUPPLIED

1. Modification of the description statement to is a clear, practically colorless solution for intravenous administration available as:

   - NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.

   - NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL).

2. Addition of the statement "After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrigerated 10 mL vial after 30 days after first puncture".
3. Addition of fourth column in the storage conditions table "Opened (After First Puncture) 30 days".

10 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days

4. Modification of revision date from 11/15 to 12/16.

Comment: These expected changes are associated with the new strength provided for in this supplement and conform to applicable regulations.

DOSE AND ADMINISTRATION (Full PI and Highlights)

5. Revised the statement "Dilute Vasostrict in normal saline…" in Full PI- Section 2.1 to read "Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use for intravenous administration."

Comment: This is an editorial change and is acceptable.

DOSAGE FORMS AND STRENGTHS (Highlights)

6. Revised to Injection: 20 units per mL (3)

DOSAGE FORMS AND STRENGTHS (Full PI)

7. Modification of the description statement to "is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial".

Comment: These are editorial changes and are acceptable.

Carton Label:

The new 200 Units per 10 mL labels are patterned after the approved 20 Units per mL container labels

1. Modification of strength to 200 Units per 10 mL (20 units per mL)
2. Modification of content statement to "10 mL Multiple Dose Vial". (21 CFR 201.57)
3. Modification of the NDC to 42023-190-01 (21 CFR 201.2 and 21 CFR 207.35(b)
4. Modification of storage statement to "Store between 2°C and 8°C (36°F and 46°F). Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months. Avoid freezing. 21 CFR 201.57(c)(17).

Comment: These expected changes are associated with the new strength provided for in this supplement and conform to applicable regulations.

5. Revision of dosage statement to "After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days".
6. Modification of revision date from 11/15 to 7/16.
7. Modification of barcode number to 4202319001
8. Modification of product # to 3003601A and UC190J-52-90-02

Comment: These are editorial changes and are acceptable.

9. Modification of label color to blue.

Comment: Acceptable.

Immediate Container Label:

The new 200 Units per 10 mL labels are patterned after the approved 20 Units per mL container labels

1. Modification of strength to 200 Units per 10 mL (20 units per mL)
2. Modification of content statement to "10 mL Multiple Dose Vial". (21 CFR 201.57)
3. Modification of the NDC to 42023-190-01 (21 CFR 201.2 and 21 CFR 207.35(b)
4. Modification of storage statement to "Store between 2°C and 8°C (36°F and 46°F). Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months. Avoid freezing. 21 CFR 201.57(c)(17).

Comment: These expected changes are associated with the new strength provided for in this supplement and conform to applicable regulations.

5. Revision of dosage statement to "After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days".
6. Modification of revision date from 11/15 to 7/16.
7. Modification of barcode number to (01)00342023190017

8. Modification of product # to 3003602A and LA190J-52-90-02

Comment: These are editorial changes and are acceptable.

9. Modification of label color to blue.

Comment: Acceptable.

Recommendations

The changes to the content of labeling and immediate container labels are acceptable. The supplement is recommended for approval.

Yvonne Knight
Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality

Benjamin Danso
Branch Chief (Acting), Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

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Yvonne Knight

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Laya Keyvan

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 15, 2016
Requesting Office or Division:	Office of Product Quality (OPQ)
Application Type and Number:	NDA 204485/S-004
Product Name and Strength:	Vasostrict (vasopressin) Injection, 20 units per mL, and 200 units per 10 mL (20 units per mL)
Submission Date:	December 9, 2016
Applicant/Sponsor Name:	PAR Sterile Products LLC
OSE RCM #:	2016-2236-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Office of Product Quality (OPQ) requested that we review the revised prescribing information (PI) for Vasostrict to determine if the PI is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

After evaluation of the revised PI, we acknowledge that PAR Sterile Products LLC incorporated our recommendations. In conclusion, we find the revised PI for Vasostrict acceptable from a medication error perspective.

[1] Thomas S. Label and Labeling Review for Vasostrict (NDA 204485). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUNE 22. 13 p. OSE RCM No.: 2016-1060.

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/s/

SARAH E THOMAS
12/15/2016

CHI-MING TU
12/15/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	October 26, 2016
Requesting Office or Division:	Office of Product Quality (OPQ)
Application Type and Number:	NDA 204485/S-004
Product Name and Strength:	Vasostrict (vasopressin) Injection, 20 units per mL, and 200 units per 10 mL (20 units per mL)
Submission Date:	August 17, 2016
Applicant/Sponsor Name:	PAR Sterile Products LLC
OSE RCM #:	2016-2236
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Office of Product Quality (OPQ) requested that we review the revised container label, carton labeling, and prescribing information (PI) for Vasostrict (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

After evaluation of the revised container label and carton labeling, we acknowledge that PAR Sterile Products LLC considered our recommendations and implemented most of our recommended changes. In regards to our recommendation of ensuring the lot number and expiration date are present on the carton labeling, PAR Sterile Products LLC responded that "the lot number and expiration date will be printed on the cartons at the time of packaging the finished drug product. This information will be encoded on the bottom panel of the single pack

[a] Thomas S. Label and Labeling Review for Vasostrict (NDA 204485). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUNE 22. 13 p. OSE RCM No.: 2016-1060.

carton [redacted] (b) (4) . The word “LOT” and “EXP” are encoded for clarity and the expiration date will be located below the six digit lot number in the format MM/YY. The text will appear in white type on the single pack carton [redacted] (b) (4) We find this intended plan acceptable. In conclusion, we find the revised container label and carton labeling for Vasostrict acceptable from a medication error perspective.

However, we note that our recommendations for the PI from our previous review[a] were not implemented. We note that the Completed Response CMC Supplement letter dated 7/18/2016 in DARRTS may not include the PI recommendations, thus we don’t see PI revisions upon this resubmission. We again recommend the same recommendations in our previous review prior to approval of this NDA supplement.[a]

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/s/

SARAH E THOMAS
10/26/2016

CHI-MING TU
10/26/2016

LABEL AND LABELING REVIEW

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

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

Date of This Review:	June 22, 2016
Requesting Office or Division:	Office of Product Quality (OPQ)
Application Type and Number:	NDA 204485/S-004
Product Name and Strength:	Vasostrict (vasopressin) Injection, 20 units per mL, and 200 units per 10 mL (20 units per mL)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	PAR Sterile Products LLC
Submission Dates:	March 18, 2016 and April 1, 2016
OSE RCM #:	2016-1060
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

PAR Sterile Products LLC submitted this prior approval supplement (S-004) on March 18, 2016 to seek approval for a 10 mL multiple-dose vial presentation for Vasostrict (vasopressin). Prior to approval of Vasostrict, vasopressin was manufactured in 0.5 mL, 1 mL, and 10 mL vials from various manufacturers.

According to the Applicant, the Vasostrict 1 mL vial was marketed as a multiple-dose vial with the preservative Chlorobutanol. The Applicant sought a formulation change for the Vasostrict 1 mL vial on November 19, 2015 under NDA 204485/S-3 from a multiple-dose to a single-dose vial, with removal of the Chlorobutanol preservative. NDA 204485/S-3 was approved on March 21, 2016.

Under supplement 4, the Applicant seeks approval for the proposed Vasostrict 10 mL multiple-dose vial that is identical to the 1 mL single-dose vial formulation, except for the addition of Chlorobutanol as a preservative. On April 1, 2016, PAR Sterile Products LLC submitted an amendment to NDA 204485/S-004 to update the prescribing information (PI) for changes approved under S-3 and to add the 10 mL vial to the PI.

The Division of Cardiovascular and Renal Products consulted us to review the proposed 10 mL Vasostrict vial container label and carton labeling, as well as the updated Vasostrict PI for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Vasostrict container label, carton labeling, and PI to identify deficiencies that may lead to medication errors and areas for improvement.

Our review of the proposed Vasostrict container label and carton labeling, and PI found the strength is not expressed as the total quantity per total volume followed by the concentration per milliliter (proposed as "20 units per mL" instead of "200 units per 10 mL").

Specifically for the proposed Vasostrict container label and carton labeling, we noted that they are similar to the originally marketed 1 mL multiple-dose vial container label and carton labeling except for the notable differences in net quantity, package size, and NDC numbers. In addition, the 10 mL vial container label and carton labeling report a different timeframe (changed to 30 days from 48 hours) for use after initial entry into the vial. However, now that there are two strengths, we found inadequate differentiation between the 1 mL vial and 10 mL vial container labels and carton labeling, which can lead to selection errors.

After careful review of the proposed PI, we note the lack of information available in sections 3 and 16 to facilitate identification of the dosage form and the available strengths. Thus, we provide the associated recommendations in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Vasostrict container label, carton labeling, and PI can be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on our review, we recommend the following changes to the PI be implemented prior to the approval of this NDA supplement:

1. Revise the product strength for the 10 mL multiple-dose vial as the total quantity per total volume followed by the concentration per milliliter, such that it reads 200 units per 10 mL (20 units per mL). [1]
2. Revise the Highlights of PI-Dosage Forms and Strengths and Full PI-Sections 3 and 16 to include description of the available package sizes. For example, in PI Section 3, revise to read "Injection: 20 units per mL, single-dose vial; and 200 units per 10 mL (20 units per mL), multiple-dose vial."
3. We recommend adding appropriate information to facilitate identification of the dosage form in sections 3 and 16 of the full PI. For parenteral dosage forms, include information about color of the solution and other identifying characteristics.

[1]United States Pharmacopoeia (USP) General Chapter <1> Injections

4. Section 16 recommends to "Discard the 10 mL vial after 30 days after first puncture." Specify what storage condition applies (e.g., refrigeration or at room temperature) to the 30 days after first puncture.
5. For consistency across Highlights of PI- Dosage and Administration and Full PI-Section 2.1, revise the statement "Dilute Vasostrict in normal saline…" in Full PI- Section 2.1 to read "Dilute Vasostrict® with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration."

4.2 RECOMMENDATIONS FOR PAR STERILE PRODUCTS LLC

We recommend the following be implemented prior to approval of this NDA supplement:

A. General Recommendations (vial container label and carton labeling)
   1. Revise the product strength for the 10 mL multiple-dose vial as the total quantity per total volume followed by the concentration per milliliter, such that it reads 200 units per 10 mL (20 units per mL).[1]
   2. Revise the 10 mL container labels and carton labeling so that they (b) (4) (b) (4) between the currently marketed Vasostrict 20 units/mL product and the proposed Vasostrict 200 units/10 mL product, in order to prevent strength confusion and selection errors. In addition, consider other features that may further differentiate the container labels and carton labeling of the two different strengths of Vasostrict products.
   3. We note that the PI states "Do not freeze," but the container label and carton labeling do not contain this warning. If space allows, include the warning, "Avoid freezing," on the container label and carton labeling.
   4. The container label and carton labeling recommend to (b) (4) (b) (4) Specify what storage condition applies (e.g., refrigeration or at room temperature) to the 30 days after first puncture.

B. Container Label
   1. If space allows, we recommend removing the phrase, (b) (4) (b) (4) and adding in its place the following storage information: "Vials may be held at 20 °C to 25 °C (68 °F to 77 °F) for up to 12 months."

C. Carton Labeling
   1. Ensure the lot number and expiration date are present on the carton labeling. Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[2]
   2. Consider relocating the following statement, "Do not store above 25 °C (77 °F)." to after the statement discussing storage between 20 °C to 25 °C, as follows: "Vials may be held at 20 °C to 25 °C (68 °F to 77 °F) for up to 12 months. Do not store above 25 °C (77 °F)." This reorganization provides the appropriate action first in relation to storage at room temperature, instead of what not to do (negative statement) first.

[2]Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vasostrict (vasopressin) that PAR Sterile Products LLC submitted on April 1, 2016.

Table 2. Relevant Product Information for Vasostrict (vasopressin)	
Initial Approval Date	April 17, 2014
Active Ingredient	Vasopressin
Indication	Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
Route of Administration	Intravenous
Dosage Form	Injection
Strengths	• 20 units per mL • 200 units per 10 mL (20 units per mL)
Dose and Frequency	Dilute Vasostrict with normal saline or 5% dextrose in water to either 0.1 units per mL or 1 unit per mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. The dose for post-cardiotomy shock is 0.03 to 0.1 units per minute, and the dose for septic shock is 0.01 to 0.07 units per minute. In general, titrate to the lowest dose compatible with a clinically acceptable response. If the target blood pressure response is not achieved, titrate up by 0.005 units per minute at ten to fifteen minute intervals. After target blood pressure has been maintained for eight hours without the use of catecholamines, taper Vasostrict by 0.005 units per minute every hour as tolerated to maintain target blood pressure.
How Supplied	• Carton of 25 single dose vials each containing vasopressin 1 mL at 20 units per mL • Carton of 1 multiple dose vial containing vasopressin 10 mL at 20 units per mL (b) (4) [redacted]
Storage	Store between 2°C and 8°C (36°F and 46°F). Do not freeze. Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date,

	then the shorter date must be used. Do not use Vasostrict beyond the manufacturer's expiration date stamped on the vial. Discard the 10 mL vial 30 days after first puncture.
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 26, 2016, we searched the L:drive and AIMS using the terms vasopressin, Vasostrict, and NDA 204485 to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified six applicable label and labeling reviews[3,4,5,6,7,8], and we confirmed that our previous recommendations were implemented or considered.

[3] DeFronzo K. Label, Labeling and Packaging Review for Pitressin (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUNE 7. OSE RCM No.: 2012-2808.

[4] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 12. OSE RCM No.: 2013-2864.

[5] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 26. OSE RCM No.: 2013-2864-1.

[6] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APRIL 8. OSE RCM No.: 2013-2864-2.

[7] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 28. OSE RCM No.: 2014-1283.

[8] Gao T. Label and Labeling Review for Vasostrict (NDA 204485/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MARCH 27. OSE RCM No.: 2015-563.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On June 8, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Any of the Words: Vasostrict

D.2 Results

Our search retrieved three newsletters, of which all three of the newsletters describe a medication error potentially related to Vasostrict labels and labeling.[9,10,11] The newsletters published during 2015 describe an error involving a mix-up between vasopressin injection and desmopressin injection. Vasostrict was approved in November 2014, and unlike previous vasopressin products, required refrigeration. Therefore, vasopressin was no longer found in crash carts but in the refrigerated automated dispensing cabinets (ADC). In the error report, a patient at the hospital needed vasopressin for emergent hemodynamic decompensation. Therefore, the nurse went to the ADC to obtain vasopressin. When she tried to access the drug, an ADC refrigerator door opened, and the nurse mistakenly retrieved a desmopressin ampule, believing it was vasopressin. The medications were both present in the ADC refrigerator on separate shelves and labeled with their generic names. The patient subsequently received the wrong drug, and the nurse didn't realize the error until the order was later entered and the barcode scanned. The physician was made aware of the medication error, and the patient then received vasopressin as ordered. There were no long-term adverse effects as a result of this error.

The hospital responded by improving the labeling of bins in the refrigerator, and considered implementing an electronic dispensing alert that would warn about the problem when the drugs were removed from the ADC. In addition, after the initial error report by ISMP, PAR Sterile Products LLC received FDA approval on May 7, 2015 to extend the labeled stability of Vasostrict to one year after removal from the refrigerator. The storage information was updated on the carton labeling, and Vasostrict was able to be stocked again on crash carts. This separation in the storage requirements for Vasostrict and desmopressin may help prevent wrong drug medication errors. No further error reports related to this issue have been reported in ISMP newsletters.

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[9] Institute for Safe Medication Practices. Safety briefs: Low BP treated with desmopressin instead of vasopressin. ISMP Med Saf Alert Acute Care. 2015;20(8):3.

[10] Institute for Safe Medication Practices. Quarterly Action Agenda: Desmopressin confused with vasopressin. ISMP Med Saf Alert Acute Care. 2015;20(16):5.

[11] Institute for Safe Medication Practices. Safety briefs: Back on the crash cart. ISMP Med Saf Alert Acute Care. 2015;20(11):6.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 26, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with Vasostrict (vasopressin) label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[12]

Table 3: FAERS Search Strategy	
Date Range	**Initial FDA Rcvd. Date From: 20140417** **Initial FDA Rcvd. Date To: N/A**
Product	**Vasopressin** [active ingredient]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified seven cases, of which one case described an error relevant for this review and could potentially be addressed by label and labeling revisions. The relevant case has an initial FDA received date of June 25, 2015 and is the same error report retrieved from the ISMP newsletters[9,10,11] and discussed in Appendix D.

[12] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

E.3 List of FAERS Case Numbers

FAERS case number and manufacturer control number for the case relevant for this review:

- FAERS case number: 11220359
- Manufacturer control number: not provided

E.4 Description of FAERS

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

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[13] along with postmarket medication error data, we reviewed the following Vasostrict (vasopressin) label and labeling submitted by PAR Sterile Products LLC on March 18, 2016 and April 1, 2016.

- Container label submitted on March 18, 2016
- Carton labeling submitted on March 18, 2016
- Prescribing information submitted on April 1, 2016 (not shown)

G.2 Label and Labeling Images

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full immediately following this page.

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

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/s/

SARAH E THOMAS
06/22/2016

CHI-MING TU
06/22/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Darrell Lyons & Tri Minh Bui-Nguyen
OMPT/CDER/OSE/PMS

Mail: OSE

FROM: Yvonne Knight, OPRO, (301) 796-2133

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/15/16		204485	S-004	8/17/16

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vasostrict Injection	PAS (Resubmission)		12/2/16

NAME OF FIRM: PAR Sterile Products LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The supplement is a resubmission that provides for a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product. The supplement addresses DMEPA deficiencies.

SIGNATURE OF REQUESTER Yvonne Knight	METHOD OF DELIVERY (Check all that apply) ☐ MAIL x DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

YVONNE L KNIGHT
09/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Darrell Lyons & Tri Minh Bui-Nguyen
OMPT/CDER/OSE/PMS

Mail: OSE

FROM: Yvonne Knight, OPRO, (301) 796-2133

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/6/16		204485	S-004	3/18/16

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vasostrict Injection	PAS		6/24/16

NAME OF FIRM: PAR Sterile Products LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- x LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The supplement provides for a 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply)
Yvonne Knight	☐ MAIL x DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

YVONNE L KNIGHT
05/06/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204485/S-004

ACKNOWLEDGEMENT –
PRIOR APPROVAL SUPPLEMENT

Par Sterile Products, LLC
Attention: Carla English, Senior Manager Regulatory Affairs
One Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. English:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	204485
SUPPLEMENT NUMBER:	004
PRODUCT NAME:	Vasostrict® (vasopressin injection, USP)
DATE OF SUBMISSION:	March 18, 2016
DATE OF RECEIPT:	March 18, 2016

This "Prior Approval" supplemental application proposes the following change:

- 10 mL multiple dose vial presentation utilizing a new formulation for the finished drug product.

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 May 17, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be July 18, 2016.

SUBMISSION REQUIREMENTS

Cite the application 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

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, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions please feel free to call me at (301) 796-2133.

Sincerely,

Yvonne L. Knight -S

Digitally signed by Yvonne L. Knight -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001233266, cn=Yvonne L. Knight -S
Date: 2016.05.02 10:39:26 -04'00'

Yvonne Knight, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration