

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**204485Orig1s003**

*Trade Name:* VASOSTRICT

*Generic or Proper Name:* Vasopressin injection

*Sponsor:* PAR Sterile Products LLC.

*Approval Date:* April 17, 2014

*Indication:* Vasostriect is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post cardiectomy or sepsis) who remain hypotensive despite fluids and catecholamines.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 204485Orig1s003

### CONTENTS

#### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	
<b>REMS</b>	
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology / Virology Review(s)</b>	<b>X</b>
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Other Reviews</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s003**

**APPROVAL LETTER**



NDA 204485/S-003

**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 November 19, 2015, received November 19, 2015, 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 January 13, 2016 and March 10, 2016.

This “Prior Approval” supplemental new drug application provides for a change in formulation in the finished drug product and revisions to the drug product specifications.

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

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 packaging 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).

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, 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-003.**” 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: 2016.03.18 16:19:34 -04'00'

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



**Vasostriect®**  
(vasopressin injection, USP)  
For Intravenous Infusion

30036619

**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®.

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

**INDICATIONS AND USAGE**

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

**DOSAGE AND ADMINISTRATION**

- Dilute Vasostriect® 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; packaged as 1 mL per vial (3)

**CONTRAINDICATIONS**

- Vasostriect® 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, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

**DRUG INTERACTIONS**

- Pressor effects of catecholamines and Vasostriect® are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostriect®. (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: 11/2015

**FULL PRESCRIBING INFORMATION: CONTENTS\***

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
  - 2.1 Preparation of Diluted Solutions
  - 2.2 Administration
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
  - 5.1 Worsening Cardiac Function
- 6 ADVERSE REACTIONS
- 7 DRUG INTERACTIONS
  - 7.1 Catecholamines
  - 7.2 Indomethacin
  - 7.3 Ganglionic Blocking Agents
  - 7.4 Furosemide
  - 7.5 Drugs Suspected of Causing SIADH
  - 7.6 Drugs Suspected of Causing Diabetes Insipidus
- 8 USE IN SPECIFIC POPULATIONS
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
- 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
  - 12.1 Mechanism of Action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING

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

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

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

**2 DOSAGE AND ADMINISTRATION**

**2.1 Preparation of Diluted Solutions**

Dilute Vasostriect® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. 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	
		Vasostriect®	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 Vasostriect® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

**3 DOSAGE FORMS AND STRENGTHS**

Injection: 20 units per mL; packaged as 1 mL per vial

**4 CONTRAINDICATIONS**

Vasostriect® 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 Vasostriect® 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 Vasostriect® on mean arterial blood pressure [see *Clinical Pharmacology* (12.3)].

**7.4 Furosemide**

Use with *furosemide* increases the effect of Vasostriect® 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, methyl dopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasopressin®.

## 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 Vasopressin®.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

**Risk Summary:** There are no adequate or well-controlled studies of Vasopressin® 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 Vasopressin® 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.

Vasopressin® 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 Vasopressin® 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

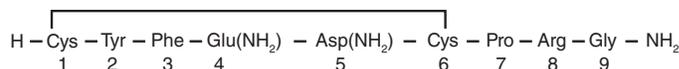
Overdosage with Vasopressin® can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, 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. Vasopressin® 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 chemical name of vasopressin is Cyclo (1-6) L-Cysteiny-L-Tyrosyl-L-Phenylalanyl-L-Glutamyl-L-Asparaginy-L-Cysteiny-L-Prolyl-L-Arginy-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: C<sub>46</sub>H<sub>85</sub>N<sub>15</sub>O<sub>12</sub>S<sub>2</sub>

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<sub>1</sub> receptors. Vascular V<sub>1</sub> receptors are directly coupled to phospholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V<sub>2</sub> receptors which are coupled to adenylyl 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<sub>1</sub>-receptors and release of prolactin and ACTH via V<sub>3</sub> receptors. At lower concentrations typical

for the antidiuretic hormone vasopressin inhibits water diuresis via renal V<sub>2</sub> 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<sub>1/2</sub> 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, carboxypeptidase and disulfide oxidoreductase cleave vasopressin at sites relevant to 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, alfentanil and sufentanil 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

Vasopressin® (vasopressin injection, USP) is supplied in vials as follows:

A carton of 25 single dose vials each containing vasopressin 1 mL at 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 Vasopressin® beyond the manufacturer's expiration date stamped on the vial.

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)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier

NDC 42023-164-25 (carton)

Distributed by:  
**Par Pharmaceutical Companies, Inc.**  
Chestnut Ridge, NY 10977

R11/15

OS164J-01-90-04

Vasopressin® is a registered trademark of Par Pharmaceutical Companies, Inc.

NDC 43223 104 01 Rx Only  
**Vasotristic®**  
(Vasopressin Injection, USP)  
**20 Units per mL**

For Intravenous Infusion  
Must be diluted prior to use  
Store between 2°C and 8°C  
(32°F and 46°F). Do not store  
above 25°C (77°F).

1 mL Single-Dose Vial

Discontinue use if precipitation  
is observed.  
For more information, contact  
Parke-Davis Pharmaceutical Co., Inc.  
Dearborn, Michigan, 48124  
R-1110 038132 5022



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LOT

EXP

1 mL x 25 Single Dose Vials

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

**20 Units per mL**

**Vasostriect®**  
 (Vasopressin Injection, USP)

Rx Only

NDC 42023-164-25

NDC 42023-164-25 Rx Only

**Vasostriect®**  
 (Vasopressin Injection, USP)

**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). Do not store above 25°C (77°F).  
 Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months.

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1 mL x 25 Single Dose Vials

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

**20 Units per mL**

**Vasostriect®**  
 (Vasopressin Injection, USP)

Rx Only

NDC 42023-164-25

NDC 42023-164-25 Rx Only

**Vasostriect®**  
 (Vasopressin Injection, USP)

**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). Do not store above 25°C (77°F).  
 Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s003**

**CHEMISTRY REVIEW(S)**

<b>CHEMIST'S REVIEW:</b>	<b>1. ORGANIZATION:</b>	<b>2. NDA Number: 204-485</b>
<b>3. Name and Address of Applicant (City &amp; State):</b> Par Sterile Products 1 Ram Ridge Road Chestnut Ridge, New York 10977	<b>4. Supplement(s):</b> <b>Number(s)</b> <b>Date(s)</b> S-003                      11/19/15	
<b>5. Drug Name:</b> Vasostriect®	<b>6. Nonproprietary Name:</b> Vasopressin	<b>7. Amendments: - Dates</b> S-003                      1/13/15
<b>8. Supplement Provides For:</b> formulation change as well as revisions in the drug product specifications.		
<b>9. Pharmacological Category:</b> To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.	<b>10. How Dispensed:</b> Rx	<b>11. Related NDAs:</b>
<b>12. Dosage Form(s):</b> Injection	<b>13. Potency:</b> 1 mL vial (20 units per mL)	
<b>14. Chemical Name and Structure:</b> <u>Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide.</u>		<b>15. Records/Reports:</b> <b>Current</b> <b>Yes</b> <b>X</b> <b>No</b> <b>Reviewed</b> <b>Yes</b> <b>No X</b>
<p>Molecular Formula: C<sub>46</sub>H<sub>65</sub>N<sub>15</sub>O<sub>12</sub>S<sub>2</sub> Molecular weight: 1084.23 One mg is equivalent to 530 units</p>		
<b>16. Comments:</b> This is a <b>PA</b> supplement. The approved product is supplied in a 1 mL multi-dose vial containing vasopressin 20 units/mL, Chlorobutanol as a preservative, water for injection, and acetic acid for pH adjustment. In this submission the applicant is proposing formulation change (b)(4). The formulation changes include establishing a new pH limit, the addition of sodium acetate for buffering, and the removal of Chlorobutanol. Micro has <b>recommended</b> for approval on the basis of sterility assurance (Eric Adeeku, Ph.D., dated 3/16/2016).		
<b>17. Conclusions and Recommendations:</b> The supplement is “ <b>approved</b> ” from the standpoint of chemistry, manufacturing and controls.		
<b>18. Reviewer:</b>		
<b>Name:</b> Kris Raman, Ph.D. Sr. CMC Reviewer	<b>Signature:</b>	<b>Date Completed:</b> 3/18/2016

**REVIEW NOTES**

Par Sterile Products is submitting this *Prior Approval Supplement* seeking approval for a formulation change in the finish drug product.

The approved product is supplied in a 1 mL multi-dose vial containing vasopressin 20 units/mL, Chlorobutanol as a preservative, water for injection, and acetic acid for pH adjustment. Formulation development studies were undertaken to (b) (4) in (b) (4). These studies provide the basis for development of a new formulation establishing a new pH limit, the addition of sodium acetate for buffering, and the removal of Chlorobutanol.

The proposed finished drug product specifications are similar to those approved in the original NDA but account for the removal of Chlorobutanol in the formulation, update to the pH release limits. (b) (4) (b) (4)

(b) (4)

In support of this *Prior Approval Supplement*, the applicant has provided the following information in this submission:

1. Drug substance data related to the exhibit batches.
2. Information on Sodium acetate, (b) (4)
3. Proposed drug product specification, Certificates of Analyses for three exhibit batches (Lot RC3279, Lot RC3280, and Lot RC3281). These certificates of analyses are included in section 3.2.P.5.4 of this submission.
4. Post Approval Stability Protocol and supportive stability data for the three exhibit batches up to 3 months.
5. Executed batch records.
6. Updated labeling including revised carton, vial label and package insert.

**DRUG SUBSTANCE:**

(b) (4)

14 Pages have been Withheld in Full as b4 ( CCI/ TS ) immediately following this page.

## Stability Protocol for Annual Stability Batches:

Shelf Life Condition: 5±3°C\*

Test	Procedure	Samples Per Test	Interval (Months)						
			0	3	6	9	12	18	24
Description	(b) (4)	1	R	X	X	X	X	X	X
pH		20	R	X	X	X	X	X	X
Assay (HPLC)		1	R	X	X	X	X	X	X
Related Substances		0	R	X	X	X	X	X	X
Particulate Matter (USP <788> Method 1)		30	R	X	X	X	X	X	X
Bacterial Endotoxin		2	R	N/A	N/A	N/A	N/A	N/A	X
Sterility		40	R	N/A	N/A	N/A	X	N/A	X
<b>Total Samples per Study (1.3X):</b>								512	

\* Inverted orientation only

X= Test performed, NA= Test not performed, R= Release results used for time 0

### Comment:

The 3 month stability data for three registration batches of the new formulation Vasostrict® (vasopressin injection, USP) at 5°C and 25°C were evaluated. Based on the trends observed in these studies in comparison to the studies of the current approved product and development studies, the quality attributes of the proposed new formulation of Vasostrict 1 mL are expected to remain consistent with the proposed limits with the same storage conditions. The data supports a 24 month refrigerated (2°C to 8°C) shelf life with a 12 month period out of refrigeration at USP controlled room temperature storage condition anytime within the labeled shelf life.

### Shelf Life:

The approved shelf life of Par's current 1 mL presentation Vasostrict® (vasopressin injection, USP) is 24 months at 2-8°C with a Time Out of Refrigeration (ToR) period of up to 12 months at USP controlled room temperature during the 24 month shelf life.

Based on available stability data 24 months shelf life can be granted when stored at 2-8°C with a Time Out of Refrigeration (ToR) period of up to 12 months at USP controlled room temperature during the 24 month shelf life.

### LABELING:

#### 11 DESCRIPTION

##### Current:

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, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6.

##### Revised to:

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.

**Proposed Container Label**



**Proposed Carton Label**



**Conclusion:** The supplement is approved from the CMC perspective.

Krishna  
P. Raman  
-S

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P. Raman -S  
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Government, ou=HHS,  
ou=FDA, ou=People,  
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1300180736, cn=Krishna P.  
Raman -S  
Date: 2016.03.18 15:12:36  
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Ramesh  
Raghavachari -S

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cn=Ramesh Raghavachari -S  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s003**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

March 16, 2016

**NDA:** 204485/S-003

**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
11/19/2015	11/19/2015	N/A	02/11/2016
03/10/2016	03/10/2016	N/A	03/16/2016

**Submission History (for 2<sup>nd</sup> Reviews or higher)**

None

**Applicant/Sponsor**

**Name:** Par Sterile Products, LLC

**Address:** One Ram Ridge Road, Chestnut Ridge, NY 10977

**Representative:** Carla English, Senior Manager, Regulatory Affairs

**Telephone:** 845-573-5728

**Fax:** 845-573-5795

**Name of Reviewer:** Eric K. Adeeku, Ph.D.

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

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Prior approval supplement
  2. **SUBMISSION PROVIDES FOR:** a change in formulation
  3. **MANUFACTURING SITE:**  
JHP Pharmaceuticals LLC  
870 Parkdale Road,  
Rochester, MI 48307, USA
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**  
Sterile injection for continuous intravenous infusion, 1 mL single dose vial containing 20 units/ml vasopressin.
  5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)  
[REDACTED] (b) (4).
  6. **PHARMACOLOGICAL CATEGORY:** Treatment of vasodilatory (post-cardiotomy and septic) shock

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** N/A

The approved formulation of this 1 mL multi-dose drug product contains 20 units/mL vasopressin, preservative Chlorobutanol, WFI and acetic acid for pH adjustment. It is packaged in single dose vials but dilution storage studies are provided. [REDACTED] (b) (4)

[REDACTED] a new formulation with a new pH limit that employs the addition of Sodium acetate for buffering and the removal of chlorobutanol is proposed.

Goal date is 03/19/2016

Response to the Agency's 03/07/2016 information request was provided in the 03/10/2016 submission.

Filename: 204485s3.doc

Template version: OGD modified\_AP\_2014v6.doc

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** - This 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** – N/A
- 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.

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
Microbiologist: Eric K. Adeeku, Ph.D.  
Microbiology Secondary Reviewer: Jesse Wells, Ph.D.
- C. CC Block**  
cc: Field Copy

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(b) (4)

Acceptable

Eric K. Adeeku -A Digitally signed by Eric K. Adeeku -A  
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ou=FDA, ou=People, cn=Eric K. Adeeku -A,  
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Date: 2016.03.16 12:00:15 -04'00'

Jesse Wells -S Digitally signed by Jesse Wells -S  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s003**

**OTHER REVIEW(S)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**  
**Review #1**

**Office of Program and Regulatory Operations**

**Application Number: NDA 204485/S-003**

**Name of Drug: Vasostriect® (vasopressin injection, USP)**

**Applicant: PAR Sterile Products**

**Material Reviewed:**

<b>Material</b>	<b>Submit Date</b>	<b>Receipt Date</b>	<b>Compared to</b>
Content of Labeling (SPL)	11/19/15	11/19/15	2/12/15 (last approved 5/5/15 in S-002)
Carton	11/19/15	11/19/15	2/12/15 (last approved 5/5/15 in S-002)
Immediate Container Labels	11/19/15	11/19/15	6/3/14 (last approved 9/18/14 in S-001)

**Background and Summary**

This PAS supplement was received on November 19, 2015, and provides for a formulation change in the finish drug product. In addition, a type C teleconference meeting was held on January 12, 2016, to discuss the revision of (b) (4) (b) (4). During the industry teleconference PAR stated that the current release specifications listed within the NDA were due to a typographical error. The Agency noted that even if the current release specifications were due to a typographical error, a Prior Approval Supplement is required to change the specifications. As a result, PAR requested to amend their current in-house Prior Approval supplement (NDA 204485/S-003) with the change request. The supplement was amended on January 13, 2016. CMC review recommends approval.

**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. Modified storage conditions to include “20°C to 25°C (68°F to 77°F) and Do not store above 25°C (77°C)” in the storage conditions table under Unopened Room Temperature.
2. Modified storage conditions table to include, “2°C to 8°C (36°F to 46°F) under Unopened Refrigerated column.

**Comment: Acceptable per 21 CFR 201.57(c)(17).**

3. Modification of manufactured city “Spring Valley, NY” to distributed city Chestnut Ridge, NY”. (21 CFR 201.1(h) (5)).

**Comment: Acceptable.**

4. Removal of third column in the storage conditions table “Opened (After First Puncture) 48 hours”.
5. Removal of the statement, “Discard vial after 48 hours after first puncture”.
6. Modification of revision date from 3/15 to 11/15.

**Comment: These are editorial changes and are acceptable.**

**DESCRIPTION**

1. Modification of the description statement to remove “chlorobutanol, NF 0.5% as a preservative”.

**Comment: This is an editorial change and is acceptable.**

**Carton Label:**

1. Modified storage conditions to include “Do not store above 25°C (77°C)”. (21 CFR 201.57(c)(17))
2. Modification of manufactured city “Spring Valley, NY” to distributed city Chestnut Ridge, NY”. (21 CFR 201.1(h) (5)).

**Comment: Acceptable.**

1. Removal of the statement “After initial entry into the vial, the remaining contents must be used within 48 hrs.”
2. Removal of the statement “Contains 0.5% chlorobutanol as a preservative.”
3. Addition of the statement, “Preservative free.”

**Comment: These are editorial changes and are acceptable.**

**Immediate Container Label:**

1. Modified storage conditions to include “Do not store above 25°C (77°C)”. (21 CFR 201.57(c)(17))
2. Modification of manufactured city “Spring Valley, NY” to distributed city Chestnut Ridge, NY”. (21 CFR 201.1(h) (5)).

**Comment: Acceptable.**

3. Removal of the statement, “After initial entry into the vial, the remaining contents must be used within 48 hours.”
4. Modification of revision date from 3/15 to 11/15.
5. Modification of the control number to 3003621.

**Comment: These are editorial changes and are acceptable.**

**Recommendations**

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

**Yvonne L. Knight**  
-S

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cn=Yvonne L. Knight -S  
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Yvonne Knight  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations

Date

**Benjamin Danso -S**

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

Date

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s003**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Re-assigned to DPMA1 Branch 2 reviewer.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LYUDMILA SOLDATOVA  
02/23/2016



NDA 204485/S-003

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Par Sterile Products, LLC  
Attention: Gerald Vasquez  
Associate Director, Regulatory Affairs  
One Ram Ridge Road  
Chestnut Ridge, NY 10977

Dear Mr. Vasquez:

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:** 003  
**PRODUCT NAME:** Vasostrict (vasopressin) Injection USP, 1 mL/vial  
**DATE OF SUBMISSION:** November 19, 2015  
**DATE OF RECEIPT:** November 19, 2015

This supplemental application, submitted as a "Prior Approval Supplement," proposes a formulation change and revisions in the Drug Product (DP) specifications.

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 January 19, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be March 19, 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, contact Yvonne Knight, Regulatory Business Process Manager, at (301) 796-2133.

Sincerely,  
**Reynolds B.  
Cantave -A  
(Affiliate)**

 Digitally signed by Reynolds B.  
Cantave -A (Affiliate)  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
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2, cn=Reynolds B. Cantave -A (Affiliate)  
Date: 2016.01.07 12:40:10 -05'00'

Reynolds B. Cantave, B.S., PharmD  
Regulatory Business Process Manager  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

**From:** [Dong, Zedong](#)  
**To:** [Raman, Kris P](#); [Knight, Yvonne](#)  
**Cc:** [Dong, Zedong](#)  
**Subject:** N204485S003 IQA DCRP KR  
**Date:** Saturday, December 19, 2015 12:19:24 PM

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Initial Quality Assessment – OLDP Division of Post Marketing Activities I  
(September, 2015)

NDA Supplement #: 204485/S007

Applicant: Par Sterile Products LLC

Product: Vasostriect

Receipt Date: 11/19/2015

PDUFA Goal Date: 03/19/2016

Final Category: PA

Consults: Product Quality Microbiology

Comments: The PA supplement provides for a formulation change as well revisions in the DP specifications. Applicant submitted formulation development report as well as validation results, together with updated DP specification and method validation results. Batch analysis results for three registration batches and three months stability data (for both long term and accelerated conditions) are submitted. Product Quality Microbiology consult is needed to review micro related development/validation results.