CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204485Orig1s020

Trade Name:	VASOSTRICT
Generic or Proper Name:	(vasopressin)
Sponsor:	PAR Sterile Products LLC
Approval Date:	April 4, 2021
Indication:	Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.

CENTER FOR DRUG EVALUATION AND RESEARCH

204485Orig1s020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

APPROVAL LETTER

NDA 204485/S-020

APPROVAL LETTER

Par Sterile Products LLC
Attention: Katharine Nowalski
Manager Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Katharine Nowalski:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 22, 2020, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict (vasopressin) injection.

This Prior Approval supplemental new drug application provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict presentations.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 (text for the prescribing information) 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 CONTAINER LABELS

Submit final printed carton and container labels that are identical to enclosed carton and 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 – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 204485/S-020.**" Approval of this submission by FDA is not required before the labeling is used.

REPORTING REQUIREMENTS

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

If you have any questions, call Lana Rossiter, Branch Chief, at (301) 796 - 6823.

Sincerely,

{See appended electronic signature page}

Gurpreet Gill-Sangha
Branch Chief, B3
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products Office of
Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

Gurpreet
Gill Sangha

Digitally signed by Gurpreet Gill Sangha
Date: 4/21/2021 04:27:01PM
GUID: 5135f2ad000117842392c50c36c7f28a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

LABELING

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 who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------
- Dilute 20 units/mL single dose vial or 200 units/10 mL (20 units/mL) multiple dose vial contents 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)
- The 20 units/100 mL, 40 units/100 mL and 60 units/100 mL single dose vials do not require further dilution prior to administration. (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/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution. (3)
  20 units/100 mL (0.2 units/mL), 40 units/100 mL (0.4 units/mL), and 60 units/100 mL (0.6 units/mL) in a single dose vials. Ready to use. (3)

----------CONTRAINDICATIONS----------
- Vasostrict® 10 mL multiple dose vial is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. The 1 mL single dose vial does not contain chlorobutanol and is therefore contraindicated only in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin. (4)

----------WARNINGS AND PRECAUTIONS----------
- Can worsen cardiac function. (5.1)
- Reversible diabetes insipidus (5.2)

----------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: 04/2021

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 who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Solution

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

Vasostrict® Solution for Dilution, 20 units/mL and 200 units/10 mL (20 units/mL)

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

Vasostrict® Premixed Solution, 20 units/100 mL (0.2 units/mL), 40 units/100 mL (0.4 units/mL), and 60 units/100 mL (0.6 units/mL)

This product does not require further dilution prior to administration.

2.2 Administration

In general, titrate to the lowest dose compatible with a clinically acceptable response.

The recommended starting dose is:

Post-cardiotomy shock: 0.03 units/minute

Septic Shock: 0.01 units/minute

Titrate up by 0.005 units/minute at 10- to 15-minute intervals until the target blood pressure is reached. There are limited data for doses above 0.1 units/minute for post-cardiotomy shock and 0.07 units/minute for septic shock. Adverse reactions are expected to increase with higher doses.

After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper vasopressin injection 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. To be used after dilution.

Vasostrict® is also available premixed as 20 units/100 mL (0.2 units/mL), 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use.

4 CONTRAINDICATIONS

Vasostrict® 10 mL multiple dose vial is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. The 1 mL single dose vial does not contain chlorobutanol and is therefore contraindicated only in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

A decrease in cardiac index may be observed with the use of vasopressin.

5.2 Reversible Diabetes Insipidus

Patients may experience reversible diabetes insipidus, manifested by the development of polyuria, a dilute urine, and hypernatremia, after cessation of treatment with vasopressin. Monitor serum electrolytes, fluid status and urine output after vasopressin discontinuation. Some patients may require readministration of vasopressin or administration of desmopressin to correct fluid and electrolyte shifts.

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

Postmarketing Experience

Reversible diabetes insipidus *[see Warnings and Precautions (5.2)]*

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. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict® on cardiac index and systemic vascular resistance. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed *[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. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed *[see Clinical Pharmacology (12.3)]*.

7.4 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®. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed

7.5 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®. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Vasostrict® use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with vasopressin.

Clinical Considerations

Dose adjustments during pregnancy and the postpartum period: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict® may need to be increased *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Maternal adverse reactions: Vasostrict® may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.2 Lactation

There are no data on the presence of vasopressin injection in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.

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.

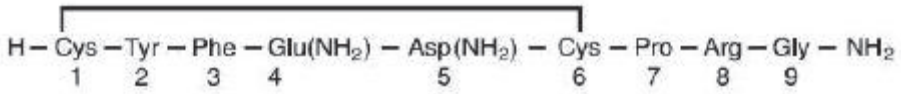
11 DESCRIPTION

Vasopressin is a polypeptide hormone. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration.

The 1 mL solution contains vasopressin 20 units/mL, 1.36 mg sodium acetate buffer and Water for Injection, USP. The 10 mL solution contains vasopressin 20 units/mL, 1.36 mg sodium acetate buffer, chlorobutanol, NF 0.5% as a preservative and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.

The 100 mL solution contains vasopressin 0.2 units/mL, 0.4 units/mL, or 0.6 units/mL. Each mL of the 0.2 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Each mL of the 0.4 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Each mL of the 0.6 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust 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

Vasopressin causes vasoconstriction by binding to V_1 receptors on vascular smooth muscle coupled to the Gq/11-phospholipase C-phosphatidyl-inositol-triphosphate pathway, resulting in the release of intracellular calcium. 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 addition, vasopressin has been demonstrated to cause vasodilation in numerous vascular beds that are mediated by V_2, V_3, oxytocin and purinergic P2 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. The pressor effect reaches its peak 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

Vasopressin plasma concentrations increase linearly with increasing infusion rates from 10 to 200 µU/kg/min. Steady state plasma concentrations are achieved after 30 minutes of continuous intravenous infusion.

Distribution Vasopressin does not appear to bind plasma protein. The volume of distribution is 140 mL/kg.

Elimination

At infusion rates used in vasodilatory shock (0.01 to 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.

Metabolism
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.

Excretion
Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged into urine.

Specific 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.

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)]*.

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

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.

13.2 Animal Toxicology and/or Pharmacology

No toxicology studies were conducted with vasopressin.

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 42023-164-10: A carton of 10 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL.

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

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

NDC 42023-219-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4 units/mL).

NDC 42023-220-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 60 units/100 mL (0.6 units/mL).

NDC 42023-237-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 20 units/100 mL (0.2 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.

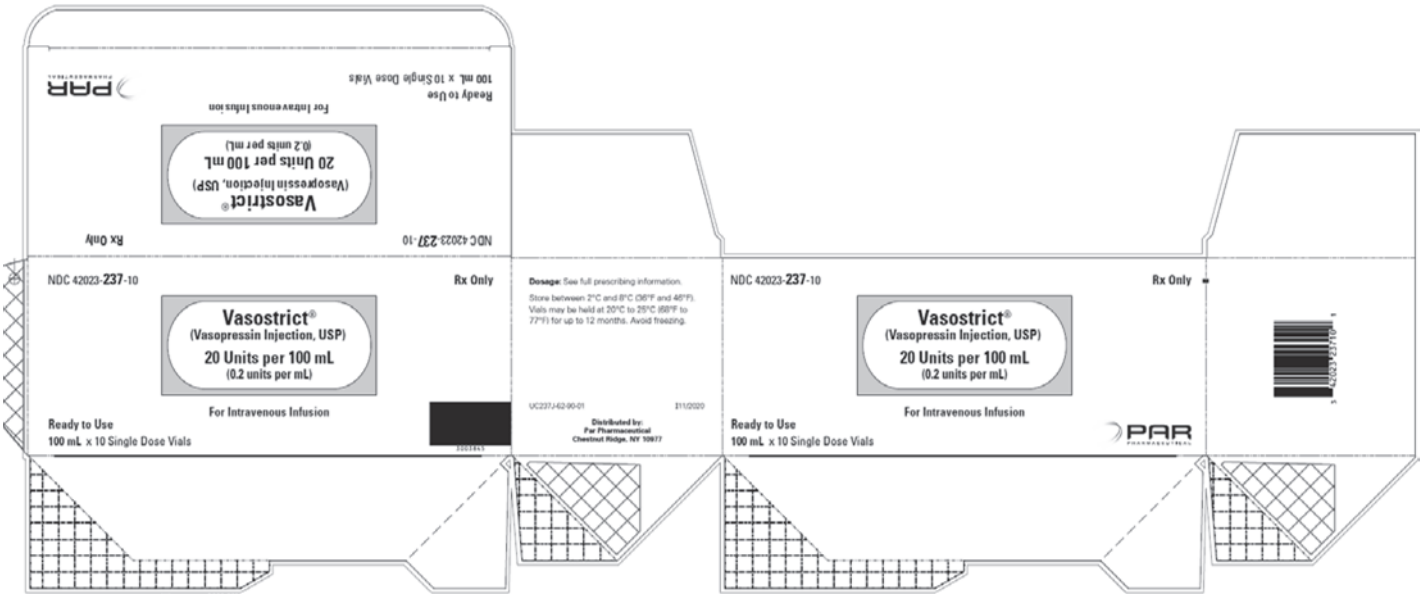
The storage conditions and expiration periods are summarized in the following table.

	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
100 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R04/2021 OS164J-01-90-XX

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


NDC 42023-237-10
Rx Only
Vasostrict®
(Vasopressin Injection, USP)
20 Units per 100 mL
(0.2 units per mL)
For Intravenous Infusion
Ready to Use
100 mL x 10 Single Dose Vials
PAR
Dosage: See full prescribing information.
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.
VC237J-62-00-01
7/11/2020
Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977
NDC 42023-237-10
Rx Only
Vasostrict®
(Vasopressin Injection, USP)
20 Units per 100 mL
(0.2 units per mL)
For Intravenous Infusion
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100 mL x 10 Single Dose Vials
PAR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 204-485/S-020**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original	PAS	12/22/2020	12/22/2020	1/1/2021	4/22/2021	4/6/2021

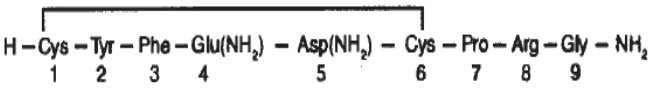
3. **Provides For:**
   Provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict® presentations.

4. **Review 1**:

5. **Clinical Review Division**:
   DCN
6. **Name and Address of Applicant**:
   Par Sterile Products, LLC
   Six Ram Ridge Road
   Chestnut Ridge, NY 10977
7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Vasostrict®	Injection	40 units/100 mL & 60 units/100 mL	Intracavernous	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	**USAN:** Vasopressin injection, US **Chemical name:** Cyclo(1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide **Molecular formula**: $C_{46}H_{65}N_{15}O_{12}S_2$ **M_W:** 1084.23 G/Mole

9. **Indication**: To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

10. **Supporting/Relating Documents**: refer to **Section III** of **CMC Assessment**.

11. **Consults**:

Consults	Recommendation	Date	Reviewer
OPMA/Facility			
DMF			
Microbiology	The submission is recommended for approval on the basis of sterility assurance.	1/8/2021	Koushik Paul, Ph.D.
Pharm/Tox	This CC system was reviewed under **S-013**. According to the PharmTox reviewer, the results of the E&L study the Vasostrict® Pre-mix for injection, suggest the exposure of the target compounds migrating from the container closure system is lower than their respective ADE/PDEs and ***considered to be safe for human use.***	3/12/2020	Rama Dwivedi, Ph.D.
Biopharm			
Statistics			
DMEPA	The proposed PI, container label and carton labeling is acceptable from a medication error perspective and DMEPA have no recommendations at this time.	3/2/2021	Maximillian Straka
CDRH/ODE			
CDRH/OC			
EA			

12. Executive Summary:
Par Sterile Products is submitting this **PA** Supplement seeking approval of a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as our current approved Vasostrict® presentations. This formulation has been identified through market intelligence as commonly prepared for use in a hospital setting from the approved 20 units/mL and 200 units/10 mL formulations. The proposed 20 units/100 mL single dose presentation will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed), in addition to the currently approved 40 units/100 mL and 60 units/mL single dose presentations.

Vasostrict® 20 units/100 mL will be produced at the same manufacturing facility as the 40 units/100 mL and 60 units/mL presentations as well as the 20 units/mL and 200 units/10 mL vial presentation (Rochester, MI). Additionally, the active pharmaceutical ingredient (API) has not changed from that which is currently approved under NDA 204-485.

Evaluation of drug product batch release data showed to meet the specification limits.

An analysis of the stability data for the Vasostrict® 20 units/100 mL formulation was performed. Based on the trends observed in these studies the quality attributes of the proposed Vasostrict® 20 units/100 mL formulation is expected to remain consistently within the proposed limits.

Microbiology was reviewed by Koushik Paul, Ph.D., (1/8/2021) and recommended for approval on the basis of sterility assurance

The proposed PI, container label and carton labeling is acceptable to DMEPA from a medication error perspective and have no further recommendations at this time.

This CC system was reviewed for extractable and leachable (**E&L**) study under **S-013** by PharmTox reviewer Rama Dwivedi, Ph.D., dated 3/12/2020. According to the PharmTox reviewer, the results of the **E&L** study the Vasostrict® Pre-mix for injection, suggest the exposure of the target compounds migrating from the container closure system is lower than their respective ADE/PDEs and ***considered to be safe for human use.***

13. Conclusions & Recommendations:

The supplement is recommended for approval from CMC perspective.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Kris Raman, Ph.D., Sr. CMC reviewer, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
Gurpreet Gill-Sangha, Ph.D., Branch Chief, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

Vasostrict is a sterile, aqueous solution of synthetic arginine vasopressin for *intravenous administration* available as 20 units/1 mL in a single dose vial, 200 units/10 mL (20 units/mL) in a multiple dose vial, 40 units/100 mL single dose vial and 60 units/100 mL single dose vial.

This supplement provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as our current approved Vasostrict® presentations. Each mL of the 0.2 unit/mL strength contains dextrose anhydrous, acetic acid, sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.

The proposed 20 units/100 mL single dose presentation will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed), in addition to the currently approved 40 units/100 mL and 60 units/mL single dose presentations.

Vasostrict® 20 units/100 mL will be produced at the same manufacturing facility as the 40 units/100 mL and 60 units/mL presentations as well as the 20 units/mL and 200 units/10 mL vial presentation (Rochester, MI). Additionally, the active pharmaceutical ingredient (API) has not changed from that which is currently approved under NDA 204-485.

II PROPOSED CHANGES

The current submission provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict® presentations.

III DATA SUBMITTED TO SUPPORT THE PROPOSED CHANGES

In support of this Prior Approval Supplement, the following items are provided with this submission:

- Proposed Labeling (Module 1)
- Batch Analysis of Drug Substance Lots Used in Registration Batches (3.2.S.4.4)
- Description and Composition of the Drug Product (3.2.P.1)
- Pharmaceutical Development (3.2.P.2)
- Drug Product Manufacturing Process and Controls (3.2.P.3)
- Excipient COAs (3.2.P.4)
- Drug Product Specification, Analytical Methods and COAs (3.2.P.5)
- Reference Standards (3.2.P.6)
- Container Closure System for 100 mL vial presentation (3.2.P.7)
- Stability Data (3.2.P.8)
- Executed Batch Records and Reconciliation Summary (3.2.R)

DRUG SUBSTANCE

The applicant has not referenced **Drug Master File** in the submission for review; however, limited information on drug substance (*specification* and *batch analyses*) is provided for review.

Control of Drug Substance

Specifications

The proposed Vasostrict® 20 units/100 mL formulation will utilize the same drug substance, vasopressin, approved under **NDA 204-485**.

Reviewer Evaluation: Acceptable
The drug substance specifications for vasopressin have not changed from those which are currently approved.

Batch Analyses

Par an (b) (4) analyses for vasopressin API lots used in the manufacture of the drug product batches **338583**, **338585**, and **350649** for the proposed Vasostrict® 20 units/100 mL are enclosed in this Section. Refer to the hyperlinks in the table below. Please note that all test results meet the acceptance criteria.

Sample Name	Manufacturer	Manufacturer's Lot #	Par's Receiving Lot #	Drug Product Batch #
Vasopressin	(b) (4)			338583
				338585
				350649

Below is the batch assay (**CoA**) for one representative batch of the drug substance from Par Pharma:

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studies, when compared to the approved Vasostrict® 20 units/mL, 1 mL, 200 units/10 mL, 40 units/100 mL and 60 units/100 mL formulations stability data were consistent and expected to remain within specification for the same storage conditions. Therefore, Par proposes an **expiration date of 24 month**s refrigerated (2-8°C) with a time out of refrigeration of **up to 12 months** at USP controlled room temperature during the 24 month shelf-life of the product.

LABELING

The following changes (highlighted) are proposed in the CMC sections of labeling:

Current Package Insert Revision Date 10/2020	Proposed Package Insert Revision Date 12/2020
----------**DOSAGE AND ADMINISTRATION**---------- • Dilute 20 units/mL single dose vial or 200 units/10 mL (20 units/mL) multiple dose vial contents 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) • The 40 units/100 mL and 60 units/100 mL single dose vials do not require further dilution prior to administration. (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/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution. (3) 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in a single dose vials. Ready to use. (3)	(b) (4)

Current Package Insert Revision Date 10/2020	Proposed Package Insert Revision Date 12/2020
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, 1.36 mg sodium acetate buffer and Water for Injection, USP. The 10 mL solution contains vasopressin 20 units/mL, 1.36 mg sodium acetate buffer, chlorobutanol, NF 0.5% as a preservative and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8. The 100 mL solution contains vasopressin 0.4 units/mL or 0.6 units/mL. Each mL of the 0.4 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Each mL of the 0.6 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.	(b) (4)

Current Package Insert Revision Date 10/2020	Proposed Package Insert Revision Date 12/2020
16 HOW SUPPLIED/STORAGE AND HANDLING Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as: NDC 42023-164-10: A carton of 10 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL. NDC 42023-164-25: A carton of 25 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL. NDC 42023-190-01: A carton of 1 multiple dose vial. Each vial contains vasopressin 10 mL at 200 units/mL (20 units/mL). NDC 42023-219-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4 units/mL). NDC 42023-220-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 60 units/100 mL (0.6 units/mL). Store between 2°C and 8°C (36°F and 46°F). Do not freeze.	(b) (4)

Evaluation: Acceptable

The applicant implemented proposed change in the labeling with respect to the new 20units/100 mL presentation.

LABELS

Draft Carton Label

(b) (4)

Draft Container Label

(b) (4)

IV RISK ASSOCIATED WITH THE PROPOSED CHANGES AND IMPACT TO PRODUCT QUALITY AND PATIENT SAFETY

Low

APPEARS THIS WAY ON ORIGINAL

Krishna Raman

Digitally signed by Krishna Raman
Date: 4/07/2021 05:12:13PM
GUID: 508da7210002a0a804126eedcec07751

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 4/07/2021 09:26:15PM
GUID: 502d0913000029f375128b0de8c50020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

MICROBIOLOGY

Product Background: To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

NDA: 204485/S020

Drug Product Name / Strength: Vasopressin injection, USP (20 units/100ml single dose).

Route of Administration: Continuous Intravenous infusion.

Applicant Name: Par Sterile Products, LLC.

Manufacturing Site: Par Sterile Products, LLC 870 Parkdale Road, Rochester, MI 48307, USA.

Method of Sterilization (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only) (b) (4) **validation**

Justification (ANDA only): N/A

Review Summary: The drug product (b) (4) filled into appropriate container closure system.

List Submissions Being Reviewed: 12/22/2020.

Highlight Key Outstanding Issues from Last Cycle: N/A

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

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: Microbiology review of N204484S013MR01.doc, dated 04/10/2020, bla761146.doc, dated 01/01/2021 and (b) (4) R01.doc, dated 01/02/2020.

List Number of Comparability Protocols (ANDA only): None.

Product Quality Microbiology Assessment

Par Sterile Products, LLC submitted this PAS for seeking approval of a 20units/100ml single dose vial presentation for the same indication, route of administration and dosage form as the currently approved Vasostrict® presentations. The proposed 20units/100ml single dose presentation will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed), in addition to the currently approved 40units/100ml and 60units/ml single dose presentations (N204484S013MR01.doc, dated 04/10/2020). The applicant states that the Vasostrict® 20units/100ml will be produced at the same manufacturing facility as the 40units/100ml and 60units/100ml presentations (Rochester, MI). All the information that are required to support the proposed changes is provided below.

INFORMATION TO SUPPORT CHANGES

P.1 Description of the Composition of the Drug Product

- **Description of the Composition of the Drug Product-**
  (*32p1-description-and-composition.pdf)*

Vasostrict is a sterile, clear, colorless aqueous solution of synthetic arginine vasopressin for intravenous administration, which is supplied in a 100m (b) (4) clear glass vial with a yellow flip-off cap and available as 20units/100ml in a single dose vial presentation. The differences between the currently approved and proposed premixed presentations are provided in the *32p1-description-and-composition.pdf, page 2/4*. The drug product formulation remains unchanged and the composition of the 20units/100ml single dose vial presentation is provided below:

Table 2: Drug Product Composition

Ingredient	Grade	Function	Composition (per mL) 20 units/100 mL
Vasopressin	USP	Active Pharmaceutical Ingredient	0.2 Units
Dextrose Anhydrous	USP	(b) (4)	(b) (4)
Acetic Acid (b) (4)	USP		0.0546 mg
Sodium Acetate (b) (4)	USP		0.012 mg
Sodium Hydroxide	NF/EP	pH Adjusting Agent	QS to pH 3.8
Hydrochloric Acid	NF/EP	pH Adjusting Agent	QS to pH 3.8
Water for Injection	USP/EP	(b) (4)	(b) (4)
(b) (4)		(b) (4)	

- **Description of container closure system –**
  (*32p1-description-and-composition.pdf)*

The proposed container closure system used for the proposed 20units/100ml in a single dose vial presentation is summarized below:

Type	20 units/100 mL
Vial	100 mL, (b) (4) mm, (b) (4) ial (b) (4) Supplier: (b) (4)
Stopper	Stopper (b) (4) mm (b) (4) (b) (4) Supplier: (b) (4)
Cap	Flip-Off Cap (b) (4) mm, Yellow (Code (b) (4) (b) (4) Supplier: (b) (4)

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2 Pharmaceutical Development

(b) (4)

[redacted]

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P.8.3 Stability Data

(b) (4)

List of Deficiencies: *None*

Primary Microbiology Reviewer Name and Date:

Koushik Paul, Ph.D. and 01/07/2021

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jesse Wells, Ph.D. and 01/07/2021

Jesse Wells

Digitally signed by Jesse Wells
Date: 1/07/2021 04:24:04PM
GUID: 508da70b00028ea901ac6652677f7d00

Koushik Paul

Digitally signed by Koushik Paul
Date: 1/08/2021 04:23:18AM
GUID: 5600522e0069b02f59c7bd85b6b54742

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

OTHER REVIEW(S)

REGULATORY BUSINESS PROCESS MANAGER LABELING REVIEW

Office of Program and Regulatory Operations

Application: NDA 204485/S-020

Name of Drug: Vasostrict injection 40 units/100 mL & 60 units/100 mL

Applicant: Par Sterile Products, LLC

Submission and amendment(s) receipt date: January 8, 2021, April 8, 2021 and April 20, 2021

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to last approved labels/labeling
Prescribing Information	April 8, 2021	April 8, 2021	Last approved on March 26, 2021 in supplement 11
Carton Label	April 20, 2021	April 20, 2021	Last approved on December 17, 2016 in supplement 4
Container Label	December 22, 2020	December 22, 2020	Last approved on March 18, 2016 in supplement 3

Background and Summary Description:

This supplement provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict presentations. Based on the proposed labeling changes, a consult request was submitted to DMEPA on December 30, 2020. DMEPA review dated March 2, 2021 by Maximilian Straka, PharmD concluded that the proposed PI, container label and carton labeling is acceptable from a medication error perspective and we have no recommendations at this time.
CMC review is adequate as of April 7, 2021by Krishna Raman, PhD and Ramesh Raghavachari, PhD. An email was sent to DCN on April 19, 2021 regarding a change

within the PI for section 8: Use In Specific Populations, 8.1 Pregnancy (Risk summary) (see below email).

RE_ NDA 204485_S-020_ Requ

Review

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

The following are the assessments for each change identified:

Prescribing Information:

Highlights of Prescribing Information:

Dosage and Administration:

Last Approved: March 26, 2021 in supplement 11

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

- Dilute 20 units/mL single dose vial or 200 units/10 mL (20 units/mL) multiple dose vial contents 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)
- The 40 units/100 mL and 60 units/100 mL single dose vials do not require further dilution prior to administration. (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)

Proposed: April 8, 2021

(b) (4)

Comment:
This change is aligned with the proposed changes in the submission. Change is acceptable per CMC and DMEPA review.

Dosage Forms and Strengths:

Last Approved: March 26, 2021 in supplement 11

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

- Injection: 20 units per mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution. (3)
  40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in a single dose vials. Ready to use. (3)

Proposed: April 8, 2021

(b) (4)

Comment:

- The applicant changed the units from (b) (4) to units/mL in a single dose vial. This minor editorial change is acceptable.
- The applicant added the 20units/100mL (0.2units/mL) which is aligned with the new presentation. This change is acceptable per DMEPA and CMC reviews.

Revision Date: Changed from 3/2021 to 4/2021

Comment: Minor editorial change is acceptable. The applicant has updated the revision date for this labeling. This will be updated to approval year (04/2021).

Dosage and Administration: **Section 2.1 Preparation of Solution**

Last Approved: March 26, 2021 in supplement 11

2.1 Preparation of Solution

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

Vasostrict® Solution for Dilution, 20 units/mL and 200 units/10 mL (20 units/mL)

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

Vasostrict® Premixed Solution, 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL)

Proposed: April 8, 2021

APPEARS THIS WAY ON ORIGINAL

(b) (4)

Comment:

- The applicant added the 20units/100mL (0.2units/mL) which is aligned with the new presentation. This change is acceptable per DMEPA and CMC reviews.

Section 3: Dosage Forms and Strengths

Last Approved: March 26, 2021 in supplement 11

3 DOSAGE FORMS AND STRENGTHS

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution.

Vasostrict® is also available premixed as 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use.

Proposed: April 8, 2021

(b) (4)

Comment:
The applicant added for intravenous administration and the 20units/100mL (0.2units/mL) which is aligned with the new presentation. This change is acceptable per DMEPA and CMC reviews.

Section 8: Use in Specific Populations

Last Approved: March 26, 2021 in supplement 11

8.1 Pregnancy

Risk Summary

There are no available data on Vasostrict® use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

Proposed: April 8, 2021

(b) (4)

Comment: The applicant updated the last sentence to include with vasopressin. This change is acceptable per OND (refer to ADL email).

Section 11: Description

Last Approved: March 26, 2021 in supplement 11

11 DESCRIPTION

The 100 mL solution contains vasopressin 0.4 units/mL or 0.6 units/mL. Each mL of the 0.4 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Each mL of the 0.6 unit/mL strength also contains dextrose anhydrous, 0.0546 mg acetic acid, 0.012 mg sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.

Proposed: April 8, 2021

(b) (4)

[redacted]

Comment:
This change is aligned with the proposed changes in the submission. Change is acceptable per CMC and DMEPA review.

Section16: How Supplied/Storage and Handling

Last Approved: March 26, 2021 in supplement 11

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 42023-164-10: A carton of 10 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL.

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

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

NDC 42023-219-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4 units/mL).

NDC 42023-220-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 60 units/100 mL (0.6 units/mL).

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

Proposed: April 8, 2021

Comment:
This change is aligned with the proposed changes in the submission. Change is acceptable per CMC and DMEPA review.

Last Approved: March 26, 2021 in supplement 11

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R03/21

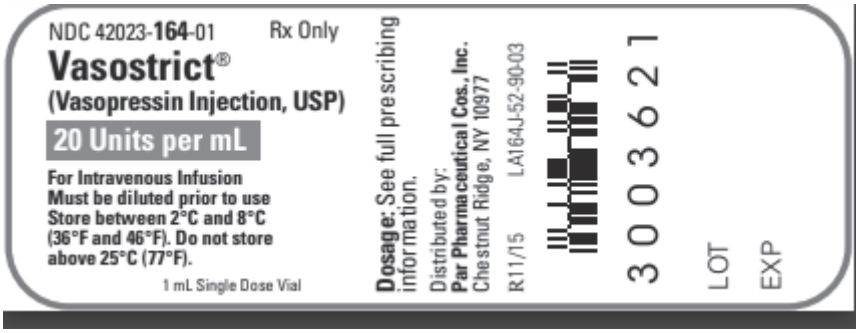
Vasostrict® is a registered trademark of Par Pharmaceutical Companies, Inc.

Proposed: April 8, 2021

Comment:
The change to the revision date and the added serial number are minor editorial changes which are acceptable.

Container

Last Approved: March 18, 2016 in supplement 3



Proposed: December 21, 2020

(b) (4)

[redacted]

Assessment:

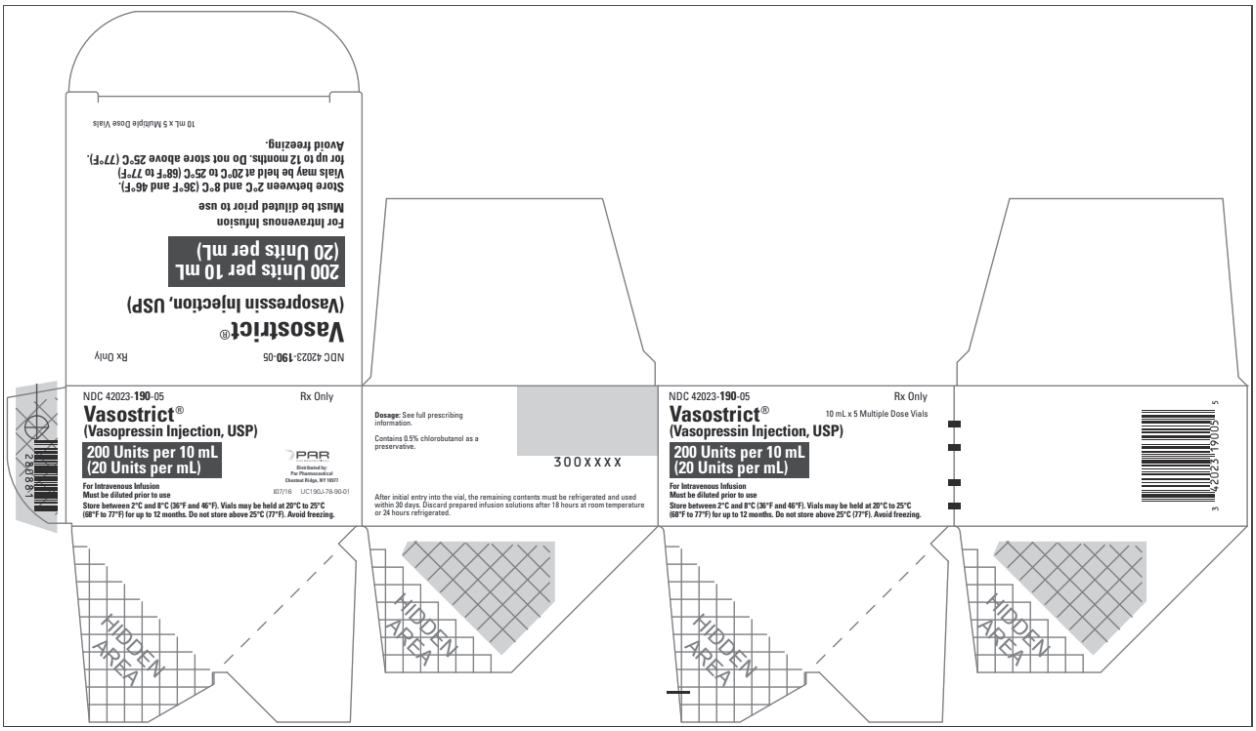
- The strength and concentration is shown by the use of a yellow colored box format in two places on the label.
- Ready to use was added to the label
- The company logo was added to the label
- The statement must be diluted prior to use was removed for the label
- The storage statement vials may be held at 20 C to 25 C for up to 12 months was added to the label

- Added Avoid Freezing to the label
- The applicant replaced Manufactured by to Distributed by PAR with a new address
- The revision date and serial number have been updated on the label

Comment: The applicant's proposed container labeling contains all required statement per regulation. Proposed changes are acceptable per DMEPA and CMC reviews.

Carton

Last Approved: December 17, 2016 in supplement 004



Proposed: April 20, 2021

Assessment:

- The strength and concentration is shown by the use of a yellow colored box format.
- The unit dose has been updated to reflect the proposed change
- Ready to use was added to the primary and back panel
- The company logo was added to the back panel
- The statement must be diluted prior to use and Do not store above 25 C (77 F) was removed for the label
- The applicant removed contains 0.5% chlorobutanol as a preservative and After initial entry into the vials, the remaining contents must be refrigerated and used within 30 days. Discard prepared infusion solutions after 18 hours at room temp or 24 hours refrigerated.
- The revision date and serial number have been updated on the label

Comment: The applicant's proposed container labeling contains all required statement per regulation. Proposed changes are acceptable per DMEPA and CMC reviews.

Enclosures:

Prescribing Information: \\CDSESUB1\evsprod\nda204485\0130\m1
Carton labels: \\CDSESUB1\evsprod\nda204485\0131\m1
Container labels: \\CDSESUB1\evsprod\nda204485\0119\m1

Recommendations

The changes to the content of labeling and labels are acceptable. The supplement is

recommended for approval.

{See appended electronic signature page}

Teicher Agosto, Pharm.D. Date
Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality

Teicher
Agosto

Digitally signed by Teicher Agosto
Date: 4/21/2021 11:07:05AM
GUID: 525da15600038cc367b38199be1ab383

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:	March 1, 2021
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204485/S-020
Product Name, Dosage Form, and Strength:	Vasostrict (vasopressin) injection, 20 units per 100 mL (0.2 units per mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	PAR Sterile Products LLC (PAR)
FDA Received Date:	December 22, 2020 and January 8, 2021
OSE RCM #:	2020-2748
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

PAR Sterile Products LLC (PAR) submitted a prior approval supplement for NDA 204485/Supplement-020 on December 22, 2020 seeking approval for a 20 units/100 mL single-dose vial presentation for the same indication, route of administration, and dosage form as the currently approved Vasostrict.

Per PAR this proposed formulation has been identified as commonly prepared for use in a hospital setting from the approved 20 units/mL and 200 units/10 mL formulations. The proposed 20 units/100 mL single-dose presentation will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed), in addition to the currently approved 40 units/100 mL and 60 units/mL single-dose presentations.

We reviewed the proposed Vasostrict prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Vasostrict (vasopressin) injection approved on April 17, 2014 is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. It is available as 20 units/mL single dose vials, 200 units/10 mL (20 units/mL) multiple dose vials, 40 units/100 mL (0.4 units/mL) single dose vials, and 60 units/10 mL (0.6 units/mL) single dose vials.

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 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 – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

PAR Sterile Products LLC (PAR) submitted prior approval supplement NDA 204485/Supplement-020 on December 22, 2020 seeking approval for a 20 units/100 mL (0.2 units/mL) single-dose vial presentation for the same indication, route of administration, and dosage form as the currently approved Vasostrict.

We note that the proposed container Labels and carton labeling utilize the same design as the currently approved 40 units/100 mL and 60 units/mL single-dose presentations, however the strength and concentration is differentiated by the use of a yellow colored box format, (i.e., yellow box for the 20 units/100 mL vial, green box for the 40 units/100 mL vial and a red box for the 60 units/100 mL vial).

We performed a risk assessment of the proposed PI, container label, and carton labeling to determine if they are acceptable from a medication error perspective.

We found the proposed PI, container label, and carton labeling acceptable from a medication error perspective. We have no further recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container label and carton labeling is acceptable from a medication error perspective and we have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vasostrict received on December 22, 2020 from PAR Sterile Products LLC (PAR).

Table 2. Relevant Product Information for Vasostrict	
Initial Approval Date	April 17, 2014
Active Ingredient	vasopressin
Indication	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
Strength	Currently approved: • 20 units per mL • 200 units per 10 mL (20 units per mL) • 40 units/100 mL (0.4 units/mL) • 60 units/100 mL (0.6 units/mL) **Proposed:** 20 units per 100 mL (0.2 units per mL)
Dose and Frequency	• [redacted] post-cardiotomy shoc [redacted] 0.03 units/minute. • For septic shock [redacted] 0.01 units/minute [redacted] titrate up by 0.005 units/minute at 10- to 15-minute intervals. • [redacted] post-cardiotomy shoc [redacted] 0.1 units/minut [redacted] 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.

<table>
<tr><td>How Supplied</td><td>

A carton of 10 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL.
A carton of 25 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL.
A carton of 1 multiple dose vial. Each vial contains vasopressin 10 mL at 200 units/10 mL (20 units/mL).
A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4 units/mL).
A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 60 units/100 mL (0.6 units/mL).
A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 20 units/100 mL (0.2 units/mL).

</td></tr>
<tr><td>Storage</td><td>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.</td></tr>
<tr><td>Container Closure</td><td>
<table>
<tr><th>Component</th><th>Proposed 20 units/100 mL Single Dose Vial Presentation</th><th>Approved 40 units/100 mL Single Dose Vial Presentation</th><th>Approved 60 units/100 mL Single Dose Vial Presentation</th><th>Approved 20 units/mL Single Dose Vial Presentation</th><th>Approved 200 units/10 mL Single Dose Vial Presentation</th></tr>
<tr><td>Vial</td><td>Vial, 100 mL, (b) (4) mm, (b) (4) Vial</td><td>Vial, 100 mL, (b) (4) mm, (b) (4) Vial</td><td>Vial, 100 mL (b) (4) mm, (b) (4) Vial</td><td>Vial, 10 mL (b) (4) (b) (4) (b) (4) mm (b) (4)</td><td>Vial, 10 mL (b) (4) (b) (4) mm (b) (4) (b) (4)</td></tr>
<tr><td>Stopper</td><td>Stoppe (b) (4) mm (b) (4) (b) (4)</td><td>Stoppe (b) (4) mm (b) (4) (b) (4)</td><td>Stopper (b) (4) mm (b) (4) (b) (4)</td><td>Stoppe (b) (4) mm (b) (4) (b) (4)</td><td>Stopper (b) (4) mm (b) (4) (b) (4)</td></tr>
</table>
</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Vasostrict and NDA 204485. Our search identified 11 previous reviews[a,b,c,d,e,f,g,h,i,j,k], and we confirmed that our previous recommendations were implemented or considered.

APPEARS THIS WAY ON ORIGINAL

[a] Jones, G. Label and Labeling Review Memo for Vasostrict (NDA 204485/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020, MAR 25, OSE RCM No.: 2019-2653-1.

[b] Jones, G. Label and Labeling Review for Vasostrict (NDA 204485/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020, MAR 16, OSE RCM No.: 2019-2653.

[c] Thomas S. Label and Labeling Memo for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 15. OSE RCM No.: 2016-2236-1.

[d] Thomas S. Label and Labeling Memo for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 25. OSE RCM No.: 2016-2236.

[e] Thomas S. Label and Labeling Review for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 22. OSE RCM No.: 2016-1060.

[f] 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.

[g] 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.

[h] 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.

[i] 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.

[j] 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.

[k] 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.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

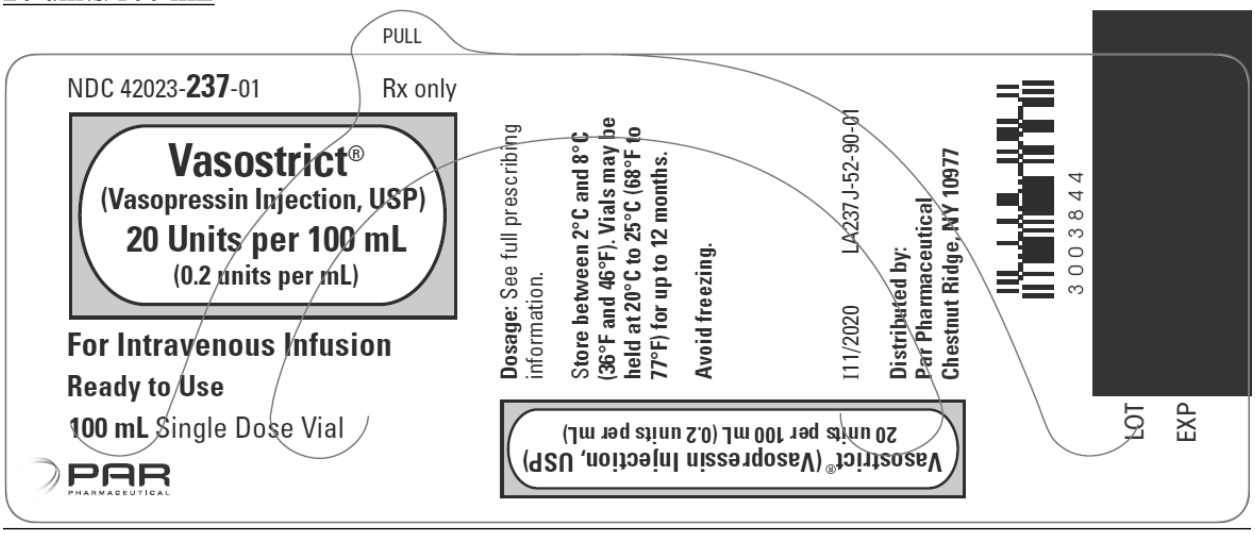
Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Vasostrict labels and labeling submitted by PAR Sterile Products LLC (PAR).

- Container label received on December 22, 2020
- Carton labeling received on December 22, 2020
- Prescribing Information (Image not shown) received on December 22, 2020, available from;
    - Tracked Changes: \\CDSESUB1\evsprod\nda204485\0119\m1\us\vasostrict-insert-side-by-side.pdf
    - Clean: \\CDSESUB1\evsprod\nda204485\0119\m1\us\vasostrict-insert-clean.doc

G.2 Label and Labeling Images

Container Labels

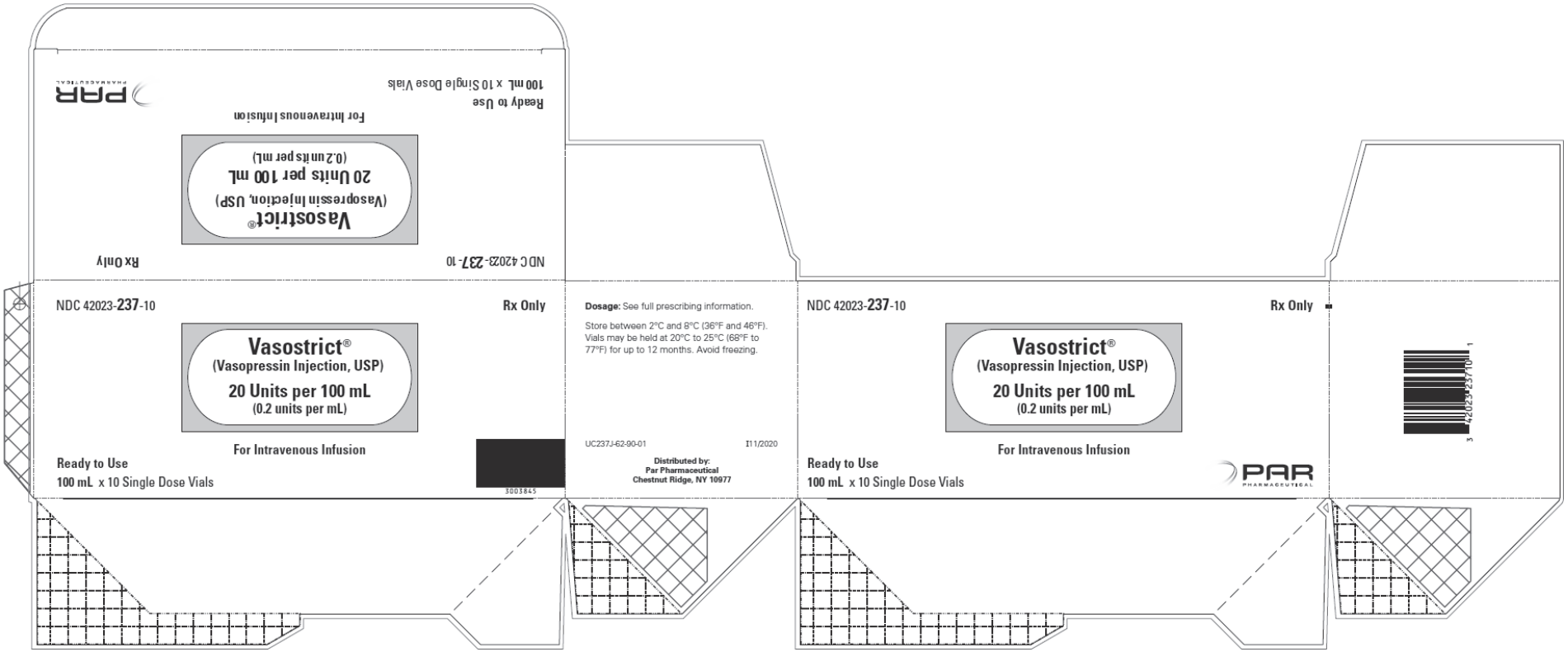
20 units/100 mL



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

Carton Labeling

20 units/100 mL



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
03/01/2021 09:31:08 AM

HINA S MEHTA
03/02/2021 02:35:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s020

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

From: Agosto, Teicher
To: Nowalski, Katharine
Subject: Information Request: NDA 204485/S-020
Date: Monday, April 19, 2021 9:58:00 PM
Attachments: image001.png

Hello,

Can you please submit an amendment to the submission with the lot and expiration date information for the carton label. We request a prompt response to this IR request no later than 12:00pm, Wednesday, April 21, 2021.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this Information Request

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best,
Teicher Agosto, Pharm D, RPh, GWCPM
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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

REQUEST FOR CONSULTATION

TO: Devi Patel, CDER/OND/OCHEN/DCN

FROM: Abolade (Bola) Adeolu, OPQ, Ext 6-4264

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/5/2021		204485/S-020	CMC PAS	12/22/2020

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vasostrict			4/15/2021

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 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 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
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
PAS provides for a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict® presentations.

Please review extractables

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Abolade (Bola) Adeolu, Ext 6-4264	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

NDA 204485/S-020

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Par Sterile Products, LLC
Attention: Katharine Nowalski
Manager, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. Nowalski:[1]

We have received your supplemental new drug application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 204485

SUPPLEMENT NUMBER: 020

PRODUCT NAME: Vasostrict (vasopressin injection, USP) 40 units/100 mL and 60 units/100 mL

DATE OF SUBMISSION: December 22, 2020

DATE OF RECEIPT: December 22, 2020

This supplemental application proposes the following change: a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as the current approved Vasostrict presentations.

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 February 21, 2021, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be April 22, 2021.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Abolade (Bola) Adeolu, OPQ, Ext 6-4264	
DATE: 12/30/2020	IND NO.	NDA NO.204485/S-020	TYPE OF DOCUMENT: CMC -Labeling	DATE OF DOCUMENT: 12/22/2020
NAME OF DRUG Vasostrict (vasopressin injection, USP) 40 units/100 mL and 60 units/100 mL	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE:3/2/2021

NAME OF FIRM: Par Pharmaceuticals

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
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ 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:

Prior Approval Supplement seeking approval of a 20 units/100 mL single dose vial presentation for the same indication, route of administration and dosage form as our current approved Vasostrict presentations.
Please review

SIGNATURE OF REQUESTER: Abolade (Bola) Adeolu, Ext 6-4264	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ■ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

If you have questions, call me, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Business Process Manager
Office of Process and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Abolade Adeolu

Digitally signed by Abolade Adeolu
Date: 1/05/2021 12:32:51PM
GUID: 508da6ea000275025a9caf8705a0d70e