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*APPLICATION NUMBER:*

**204485Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	March 20, 2014
<b>From</b>	Shari L. Targum, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA #204485
<b>Supplement#</b>	
<b>Applicant</b>	Par Sterile Products
<b>Date of Submission</b>	10/18/2013
<b>PDUFA Goal Date</b>	4/18/2014
<b>Proprietary Name / Established (USAN) names</b>	Vasostriect/Vasopressin injection, USP, synthetic
<b>Dosage forms / Strength</b>	Injection (continuous intravenous infusion): supplied as 1 mL vial, 20 Units per mL
<b>Proposed Indication(s)</b>	Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock
<b>Recommended:</b>	<i>Approval pending OC recommendation and acceptable labeling</i>

**Purpose of Cross-Discipline Team Leader (CDTL) Review**

This review is based, in part, on the following reviews:

Chemistry (Lyudmila Soldatova, 5/9/2013; 3/18/2014); Microbiology (Erika A. Pfeiler, 4/5/2013; 12/3/2013); Statistics (Fanhui Kong, 5/29/2013); Clinical (Monica L Fiszman, 5/25/2013; 2/21/2014); Clinical Pharmacology (Peter Hinderling, 5/28/2013); Biopharmaceutics /ONDQA (Elsbeth Chikhale, 3/15/2013); Pharmacology/Toxicology (Rama Dwivedi, 4/10/13), Maternal Health Team (Carrie Ceresa, Jeanine Best, Lynne P. Yao; 5/23/2013), DMEPA ( Kimberly DeFronzo, Irene Chan, Scott Dallas, 6/7/2013; Janine A. Stewart, 2/5/2014, 2/27/2014).

This review will focus on the applicant's 10/18/2013 response to a Complete Response letter (7/19/2013) and summarize major issues pertinent to approvability of this application. For additional discussion, the reader is referred to my original CDTL review (6/13/2013).

## Cross Discipline Team Leader Review Template

### 1. Introduction

On September 25, 2012, the applicant submitted a 505(b) (2) application, relying on published literature alone to support clinical pharmacology, safety and efficacy for vasopressin with a proposed indication for the treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

During the first review cycle, the microbiology, biopharmaceutics, pharmacology-toxicology, clinical pharmacology and clinical reviewers recommended approval of the vasopressin application in adults. Two disciplines, statistics and CMC, recommended against approval.

The statistical reviewer (Dr. Kong) concluded that the published literature seem to suggest that vasopressin may have an effect to increase blood pressure. However, he also concluded that the published clinical studies did not meet the standards of an “adequate and well controlled study” for conducting a confirmatory trial. Because of statistical issues, such as no pre-defined primary endpoint, multiple endpoints without multiplicity adjustment, unapproved comparator as control, and selectively reporting study results, the published studies should be viewed as exploratory. While I concur with Dr. Kong concerning the statistical issues found in the published studies, I felt that the totality of the evidence, based on consistency across studies conducted by different investigators in different institutions, was adequate to conclude that vasopressin raised systemic arterial blood pressure, and the benefit of this pressor effect lies in maintaining adequate organ perfusion and function in shock patients with low mean arterial pressure (MAP). Moreover, the safety profile of vasopressin appears to be adequately characterized, based on the literature as well as decades of use.

The CMC reviewer (Dr. Soldatova) also recommended against approval, due to multiple unresolved deficiencies. Because of these unresolved CMC issues, a “Complete Response” letter was issued on 7/19/2013, listing 20 product quality deficiencies, one clinical pharmacology deficiency related to AVP stability in diluents other than isosaline and dextrose, and requirement for a pediatric plan. This review will focus on these issues as well as additional changes made by the applicant.

On 10/18/2013, the applicant filed a response to a 7/19/2013 Complete Response letter that listed deficiencies related to product quality, clinical pharmacology and required pediatric assessments. The applicant’s requested label changes involved the following:

- Including D5W as an available diluent
- Removing statements about administering much higher doses to pregnant women during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters
- Changes to the dose titration and tapering regimens
- Changes to the cautionary statements for patients with renal and hepatic impairment
- Carton and Container labeling.

On February 20, 2014, Par Pharmaceutical Companies, Inc. acquired JHP Pharmaceuticals, LLC. On February 26, 2014, JHP Pharmaceuticals, LLC changed its name to Par Sterile Products, LLC.

## 2. Background

Vasopressin has been marketed as a therapeutic agent for nearly a century. While intramuscular or subcutaneous vasopressin is approved for the treatment of central diabetes insipidus and for the prevention and treatment of postoperative abdominal distention in abdominal roentgenography, intravenous vasopressin has been marketed but unapproved.

In June 2006, the Agency announced a new drug safety initiative to remove unapproved drugs from the market, including a final guidance entitled “Marketed Unapproved Drugs—Compliance Policy Guide (CPG).”

The applicant met with the Division of Cardiovascular and Renal Products (vasodilatory shock indication) (b) (4)

on October 17, 2011. At that time, the Division of Cardiovascular and Renal Products believed that “it may be possible to approve vasopressin without further outcome studies for increasing blood pressure in certain acute hypotensive states; however, vasopressin’s hemodynamic effects would need to be sufficiently understood to write instructions for use.”

## 3. CMC/Device

Based on information provided in the applicant’s resubmission, the CMC reviewer (Dr. Soldatova) has recommended approval of NDA 204-485 pending the overall OC recommendation. The applicant has addressed all CMC issues, and there are no unresolved deficiencies.

The major issues in the original NDA submission were: the assay acceptance criterion in the shelf life specifications, the lack of the stability data for the proposed product without overages, and the expiration period. The other issues, related to several impurities/degradants, were resolved based on the applicant’s adequate responses.

The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the CMC reviewer recommends a 12-month expiration dating period for drug product stored in the proposed container/closure system at the recommended storage condition, between 15° and 25° C (59° F and 77° F). There are no recommendations for postmarketing commitments, agreements, and/or risk management steps.

The applicant also supplied compatibility studies to support stable potency of vasopressin with D5W (1:100, or 0.2 U/mL) in ViaFlex IV bags for 26 hours at room temperature. The applicant also provided data (report DEV-13-090R, CMC review) to support compatibility of vasopressin with Ringer's, lactated Ringer's, and Plasma-Lyte® diluents.

One facility inspection was conducted on [REDACTED] (b) (4); the overall recommendation of the Office of Compliance for the manufacturing facilities is pending at the time of this review.

## 4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers of the original application concluded that vasopressin was approvable. The applicant did not provide new nonclinical pharmacology/toxicology information in this resubmission.

## 5. Clinical Pharmacology/Biopharmaceutics

During the first review cycle, the clinical pharmacology reviewer recommended approval of vasopressin. No additional clinical pharmacology review was filed; however, the reviewer (Dr. Hinderling) reviewed clinical pharmacology-related changes to the applicant's proposed labeling.

- An outstanding issue during the first cycle involved acceptable diluents for vasopressin. This issue appears to have been resolved, based on additional data from the applicant as reviewed by CMC. This vasopressin product appears to be compatible in D5W and the label has been amended accordingly.
- In the proposed labeling (submitted 3/18/2014), the applicant removed labeling language pertaining to hepatic and renal impairment. According to the clinical pharmacology reviewer, there are little published data regarding exposure in renal and hepatic impairment; however, because vasopressin administration will be titrated to effect dose adjustment will occur automatically in case the exposure is increased.
- The reviewers and the applicant reached concurrence on labeling in pregnancy, with inclusion of dosage adjustments.

## 6. Product Quality Microbiology

During the first review cycle, Dr. Erika Pfeiler, the product quality microbiology reviewer, recommended approval, with post-dilution hold times, for the drug product in 0.9% saline, of 18 hours at room temperature and 24 hours under refrigeration.

In the applicant's resubmission, the applicant provided microbiological data to support post-dilution hold times in various diluents (e.g., Lactated Ringer's USP, Plasma-Lyate A Injection USP and Ringer's Injection USP). According to Dr. Pfeiler, these studies support a maximum hold time of 18 hours at room temperature and 24 hours under refrigeration, which is the same post-dilution hold time that was determined to be adequate for dilution in 0.9% saline.

There are no unresolved issues.

## **7. Clinical/Statistical- Efficacy**

During the first review cycle, the clinical reviewer (Dr. Fiszman) recommended approval of vasopressin, as a second-line agent. Dr. Fiszman also reviewed the revised label and the pediatric study plan in the applicant's current submission.

In reviewing the label, the clinical reviewer and I proposed the following language: "Vasopressin is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines." The applicant has concurred with this proposed language.

This indication is consistent with the current guidelines,<sup>1</sup> which state that "vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP (mean arterial pressure) or decreasing NE dosage. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents.)"

## **8. Safety**

The applicant's submission did not contain new safety information.

## **9. Advisory Committee Meeting**

This application was not presented to an advisory committee meeting.

## **10. Pediatrics**

During the original NDA review, the applicant requested a full pediatric waiver from the requirement for pediatric studies under Section 505 b (a)(4)(A). The justification for the

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<sup>1</sup> Dellinger RP, Levy MM, Rhodes A et. al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Critical Care Medicine 2013; 41 (2): 580-637.

waiver request was that for the postcardiotomy shock indication, the literature data referenced supported dosing for the pediatric population. However, for the septic shock indication, “there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.” In my original review, I suggested that if this request were to be granted, labeling would likely lead to a recommendation against use in pediatric patients with septic shock.

In support of their request, the applicant cited three retrospective analyses of post-cardiotomy vasodilatory shock in pediatric patients (Alten 2012, Lechner 2007, Rosenzweig 1999) in which “the outcomes in these trials showed mixed results, and safe and effective dose levels of vasopressin were not established.” In addition, the applicant cited Choong (2009), the only randomized, controlled clinical study in pediatric patients with vasodilatory shock (78% due to sepsis).

In the Choong paper:

--Pediatric patients were randomized to receive blinded low-dose vasopressin (0.0005-0.002 U/kg/min or 0.05 U/min maximum to maintain a target MAP for age) or placebo in addition to open-label vasoactive agents. Vasoactive infusions were titrated to clinical endpoints of adequate perfusion. The primary outcome was time to vasoactive-free stability.

-- The sample size of 69 patients was calculated to achieve 90% power to detect a hazard ratio of 3, significance level of 5%; the sample size calculation assumed a 34% mortality rate and 7% dropouts or post-randomization exclusions.

--A total of 512 patients were screened, of which 403 met exclusion criteria; 35 patients were randomized to receive vasopressin, and 34 were randomized to placebo.

--There was a statistically significant increase from baseline in MAP measured one hour post-study drug (14.3 vs. 5.1,  $p=0.02$ ). This finding is consistent with a pressor effect of vasopressin. The publication did not report MAP changes at other time points.

--No real-time invasive hemodynamic measurements were captured in a majority of patients in this trial, making progression in hemodynamic status more difficult to assess.

--The median vasopressin dose was 0.04 U/min. While the paper reported that there was no statistically significant difference between groups in co-interventions for hemodynamic support during the treatment period, there was a significant difference ( $p=0.02$ ) between groups with respect to adrenal insufficiency (5 in placebo vs. 0 in vasopressin patients; Table 2); the meaning of this difference is not clear.

Choong found no significant difference between patients receiving vasopressin (N=35) and placebo (N=34) in the time to hemodynamic stability (primary outcome), organ failure-free days or ventilator-free days, length of ICU stay, and adverse events. There were 10 deaths in the AVP group compared with 5 deaths in the placebo group; in the publication, Choong reported that “none of the deaths was considered to be related to study drug” and the most frequent cause of death was refractory shock and multiple organ dysfunction. However, Choong concluded that low-dose vasopressin did not demonstrate any benefits in pediatric vasodilatory shock.

During a teleconference (April 23, 2013), the applicant explained that their rationale behind contraindicating vasopressin in the pediatric population was based on the lack of controlled

studies for postcardiotomy shock, the wide range of reported doses used, a “personal communication” from Dr. Lechner (Linz, Germany) explaining that the range of doses resulted from “trial and error” and a “personal communication” from Dr. Choong stating that she would not use AVP in this population.

The reviewers requested a full pediatric waiver from the requirement for pediatric studies based on the infeasibility of conducting such a study, rather than the safety concern based on the mortality results in the Choong study. The labeling outcomes would be that “safety and efficacy have not been demonstrated in pediatric patients.”

On May 8, 2013, the PeRC committee recommended a deferral, with a postmarketing requirement (PMR) for the applicant to provide study information (e.g., study reports, safety narratives/case report forms, protocols, datasets) from the investigators of the published pediatric studies including the Choong study; a June 26, 2013 letter to the applicant outlined this PMR.

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

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

An unresolved issue is how to label vasopressin for use in pediatric patients with vasodilatory shock.

If one were concerned about risks of vasopressin use in pediatric patients, based on the numerically higher number of deaths in the vasopressin vs. comparator group in the Choong study, one might recommend against vasopressin use in labeling. I would recommend, instead, that labeling language indicate that “safety and efficacy have not been demonstrated in pediatric patients.”

In her paper, Choong reported that the deaths were not due to study drug. Furthermore, based on the “algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in infants and children,” (Dellinger 2013) vasopressin remains a consideration in pediatric patients with warm shock and low blood pressure, who remain hypotensive despite fluids and norepinephrine. Thus, the label leaves open the possibility of vasopressin use to

maintain MAP and perfusion in hypotensive patients where the drug might be effective. The Surviving Sepsis guidelines also state that, “In the case of extremely low systemic vascular resistance despite the use of norepinephrine, the use of vasopressin and terlipressin have been described in a number of case reports, yet evidence to support this in pediatric sepsis, as well as safety data, are still lacking” (Dellinger 2013). The proposed labeling language would be consistent with current guidelines.

## **11. Other Relevant Regulatory Issues**

None.

## **12. Labeling**

The Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name for vasopressin, Vasostrict, is acceptable from a safety and promotional perspective (review filed 2/6/2014; letter 2/11/2014). The applicant’s revised carton and container labels have adequately addressed concerns about medication errors and DMEPA had no additional comments (review filed 2/27/2014).

## **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

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

- Risk Benefit Assessment

Based on the published literature, there appears to be adequate evidence that vasopressin can increase MAP in patients treated with norepinephrine in the setting of vasodilatory shock due to sepsis. As Dellinger notes, “below a threshold MAP, autoregulation in critical vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow.”

VASST, the largest randomized, controlled study of norepinephrine alone, compared to norepinephrine plus vasopressin (0.03 U/min) showed no outcome difference in the overall intent-to-treat population. A subgroup analysis showed improved survival with vasopressin (vs. no vasopressin) in patients receiving < 15 mcg/min (vs. ≥ 15 mcg/min) norepinephrine at

the time of randomization; to the best of my knowledge this finding has not been further studied in a prospective randomized, controlled trial.

The safety profile of vasopressin is based on published literature, along with decades of use. High doses of vasopressin have been associated with cardiac, digital and splanchnic ischemia. I feel that the labeling adequately addresses the risks of vasopressin; general practice dictates that patients are weaned from vasopressor therapies once hemodynamically stabilized.

I recommend routine safety surveillance, updating the label when appropriate. There is no recommended postmarketing Risk Evaluation and Management strategy or postmarketing requirements or commitments.

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03/27/2014