

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204485Orig1s000**

**MEDICAL REVIEW(S)**



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memo*

**NDA:** 204485 Vasostrict; vasopressin for vasodilatory shock.

**Sponsor:** Par Sterile Products

**Review date:** 4 April 2014

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 204485

This memo conveys the Division's recommendation to issue an Approval letter for this application.

In the first cycle, the Division issued a Complete Response (19 July 2014), citing 20 product quality issues. The applicant's response (18 October 2013) was reviewed by CMC (Soldatova, 18 March 2014). There is a supplementary CDTL memo (Targum, 27 March 2014) with which I am in full agreement. I highlight a few matters here.

All CMC product quality issues have been resolved. In addition, the sponsor provided information supporting dilution in additional bulk parenteral products, and these are satisfactory.

At the recommendation of the PeRC, we asked the sponsor to look into the feasibility of acquiring data from a study conducted in children. The sponsor did contact the author, and Dr. Targum documents their attempt. She and I are satisfied.

The sole issue affecting approvability at this point is an outstanding facility inspection.

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

/s/  
-----

NORMAN L STOCKBRIDGE  
04/04/2014

**Clinical Reviewer's Review Memorandum**  
**Mónica L. Fiszman CDER/OND/DCRP**

**NDA:** 204,485  
**Amendment #:** NA  
**Submission type:** Resubmission (SDN 18 and 21)  
**Submission date:** October 18, 2013 and December 23<sup>rd</sup> 2013.  
**Sponsor:** JHP Pharmaceutical  
**Product:** Vasopressin  
**Proposed use:**

**Background**

JHP Pharmaceuticals has resubmitted their NDA for Pitressin (NDA 204-485) in response to a DCRP CR Letter dated 7-19-13. In a meeting on 5-8-13 the PeRC had recommended a PMR for the applicant to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in this submission.

The sponsor submitted the following information for review

1-A Pediatric Study Plan (PSP)  
2-A revised label

**1-Pediatric Study Plan**

For the septic vasodilatory shock indication, the sponsor contacted Dr Karen Choong and discussed the possibility of obtaining clinical documentation for the controlled multicenter study reported in Choong et al 2009. The sponsor asked Dr Choong to inquire from her co-investigators if they would be willing to seek Research Ethics Board approval to provide the requested information to JHP or directly to FDA.

For the post-cardiotomy vasodilatory shock indication the sponsor proposed to contact pediatric cardiac surgeons in multiple North American centers which perform cardiac surgery in children and request information on their use of vasopressin in these patients and any existing institutional protocols for such use.

**DCaRP Action (Dec 6<sup>th</sup> 2013)**

In response to the PSP, the sponsor was asked to submit specific timelines for the septic shock indication. Regarding the post-cardiotomy vasodilatory shock, we did not concur with the sponsor proposal of collecting information from professionals since FDA does not rely on anecdotally collected information for labeling.

**Sponsor's response (Dec 23<sup>rd</sup> 2013)**

We received a response from the sponsor addressing our PSP comments. So far, the sponsor has not received authorization to obtain the requested information. In addition, the sponsor stated that  
“..... Informed consent forms did not authorize use of patient data to be provided to entities or organizations not specifically identified in the ICFs. Therefore, the patients’ legal guardians would need to be re-consented to authorize release of such information. Contacting these individuals would be particularly difficult in that patient enrollment in this trial was initiated over 10 years ago....”  
“..... Permission to provide study data to JHP may also need to be granted by the study’s corporate Sponsor, Ferring, Inc. Given that Ferring, Inc. is a direct competitor, authorization from Ferring, Inc. to use study data in support a competitor’s market application would likely be difficult to obtain....”

Regarding the post-cardiotomy indication, sponsor proposed to conduct literature searches for the use of vasopressin for vasodilatory shock in pediatric patients and to report all relevant findings to FDA annually as part of the annual reports for the drug product.

**DCaRP Action:** On February 6, 2014, a team meeting was held to discuss the re-submission of the PSP and next steps to follow. It was concluded that, despite the sponsor’s efforts, there were many obstacles to overcome and it was uncertain whether the information will be released. Therefore the waiver was granted.

## **2- Sponsor’s revised Label**

In the revised label, sponsor has proposed to use vasopressin as an adjunct of fluids and catecholamines rather than for refractory shock (third line). The literature does not support the use of vasopressin as first line (concomitant to fluids and catecholamines) or as a single agent therapy. There is no supporting material to suggest that AVP could be given as an adjunct to fluids and catecholamines (first and second line). This reviewer concluded that the submission material supports a refractory vasodilatory shock indication. The rationale behind this is to prevent SAEs when using high doses of catecholamines.

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

/s/  
-----

MONICA L FISZMAN  
02/21/2014



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memo*

**NDA:** 204485 Pitressin (b) (4); vasopressin for vasodilatory shock.

**Sponsor:** JHP Pharmaceuticals

**Review date:** 18 July 2013

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 204485

This memo conveys the Division's recommendation to issue a Complete Response letter for this application.

This application has been the subject of reviews of CMC (Soldatova, 9 May 2013), microbiology (Pfeiler, 8 April 2013), biopharmaceutics (Chikhale, 15 March 2013), pharmacology/toxicology (Dwivedi, 10 April 2013), clinical pharmacology (Hinderling, 24 May 2013; two documents), medical (Fizman, 25 May 2013), and statistics (Kong, 29 May 2013). There is a comprehensive CDTL memo (Targum, 13 June 2013) with which I am in full agreement. I highlight a few matters here.

Two disciplines recommended a complete response.

The statistical reviewer recommended against approval because the studies available to support approval all were from the literature. While individually, such studies are difficult to subject to the kind of scrutiny we apply to development programs, there is a high degree of consistency that vasopressin, in doses from 0.01 to 0.1 U/min, increases blood pressure in subjects with vasodilatory shock associated with sepsis or post-cardiotomy. There are 15 controlled trials, but one study has the bulk of the experience—a randomized double-blind study in subjects with sepsis and vasodilatory shock inadequately responsive to fluids and low-dose norepinephrine, in which vasopressin was compared with high-dose norepinephrine. The study failed on its primary end point, 28-day mortality, but it was not adverse, and this study contributes to understanding of the pressor effects of vasopressin. I conclude there is both adequate information to conclude the pressor effects of vasopressin and to be able to support instructions for use in vasodilatory shock.

The CMC reviewer recommended a complete response for a long series of deficiencies related to drug substance (adequacy of the DMF, inadequacy of release specifications, among others) and drug product (various acceptance tests and specifications). In considering its enforcement discretion, Drug Shortages should consider how likely it is that other manufacturers may have similar issues.

Labeling generally will recommend use of the lowest dose capable of meeting therapeutic goals, but it is not clear what one is to do other than to use it as sparingly as clinically tolerated. The risk of too aggressive vasoconstriction is ischemia, such ischemia may be difficult to detect before there is irreparable harm. Adverse events related to peripheral (skin, muscle) ischemia, to bowel ischemia, and to coronary ischemia are all reported. The high end of the recommended dose range is empirical, based on the review team's assessment of the literature.

Clearance of vasopressin is rapid (half-life of about 10 minutes) in most subjects, but it is markedly faster in late-stage pregnancy, necessitating use of higher doses in this setting.

No other disciplines raised issues with approval.

I conclude that enough information is available to support labeling to increase blood pressure, despite lack of long-term outcome data. Providing successful negotiations on the label, the sole basis for a complete response will be CMC issues. We will ask the sponsor if they can obtain data from the best of the few studies in children.

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

/s/  
-----

NORMAN L STOCKBRIDGE  
07/18/2013

## Cross-Discipline Team Leader Review

<b>Date</b>	June 12, 2013
<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>	JHP Pharmaceuticals
<b>Date of Submission</b>	September 25, 2012
<b>PDUFA Goal Date</b>	July 26, 2013
<b>Proprietary Name / Established (USAN) names</b>	Pitressin/vasopressin injection USP
<b>Dosage forms / Strength</b>	Injection (continuous intravenous infusion)/ 20 Units/1 ml vial
<b>Proposed Indication(s)</b>	Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock
<b>Recommended:</b>	<i>Complete Response</i>

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

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

Chemistry (Lyudmila Soldatova, Ramesh Sood; 5/9/2013); Microbiology (Erika Pfeiler, Stephen Langille; 4/5/2013); Statistics (Fanhui Kong, Jim Hung; 5/29/2013); Clinical (Monica Fiszman; 5/25/2013); Clinical Pharmacology (Peter Hinderling, Rajanikanth Madabushi; 5/28/2013); Biopharmaceutics /ONDQA (Elsbeth Chikhale, Angelica Dorantes; 3/15/2013); Pharmacology/Toxicology (Rama Dwivedi, Thomas Papoian; 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).

This review will summarize clinical evidence and major issues pertinent to approvability of the application.

NOTE: Vasopressin, arginine vasopressin and AVP are used interchangeably in this review.

**1. Introduction**

The sponsor, JHP Pharmaceuticals, has submitted a 505(b)(2) application, relying on published literature alone to support clinical pharmacology, safety and efficacy for vasopressin with a proposed indication in the treatment of vasodilatory shock, including post-cardiotomy shock and septic shock.

Because of multiple unresolved deficiencies, Dr. Soldatova has recommended against approval of this application in its current form from the CMC standpoint.

The microbiology, biopharmaceutics, pharmacology-toxicology, clinical pharmacology and clinical reviewers have recommended approval of the vasopressin application in adults.

Because of statistical issues, the statistical reviewer concluded that the publications should be viewed as exploratory. [REDACTED] (b) (4)

Issues of interest include the following:

- Evidence of effectiveness based on publications alone;
- Unresolved CMC issues;
- Compatibility with solutions other than normal saline and degradation of drug product;
- [REDACTED] (b) (4)
- Dosing in pregnancy;
- Use in pediatric patients:

## 2. Background

Vasodilatory shock is characterized by low arterial blood pressure (BP) and decreased tissue perfusion, resulting from decreased systemic vascular resistance. Although vasodilatory shock may result from several etiologies, the most common cause is sepsis (Landry, 2001). Since plasma catecholamines are increased and the renin-angiotensin-aldosterone system is activated in vasodilatory shock, three mechanisms have been proposed to account for the failure of vascular smooth muscle to constrict: activation of ATP-sensitive potassium channels in the plasma membrane of vascular smooth muscle cells, activation of the inducible form of nitric oxide synthetase, and deficiency of vasopressin (Landry 2001).

Septic shock involves complex interactions between the pathogen and the host immune system, resulting in activation of host defense mechanisms, release of inflammatory mediators, activation of coagulation factors, and vasodilatation. Mortality from septic shock has been reported to be between 20-50%, and poor prognostic factors include advanced age and poor prior functional status.

Cardiac surgery with cardiopulmonary bypass (CPB) can be complicated by vasodilatory shock (also called vasoplegic syndrome). Suggested risk factors for post-cardiotomy vasodilatory shock include: pre-treatment with angiotensin converting enzyme inhibitors (ACEIs), low ejection fraction, intravenous heparin, long duration on CPB, procedure type,

pre-bypass MAP, pre-CPB vasopressors, core temperature on CPB, peri-CPB hematocrit, and intraoperative use of aprotinin (Argenziano 1997, Mekontso-Dessap 2001, Levin 2009). Pitressin® (Vasopressin Injection, USP) is a sterile, aqueous solution of synthetic vasopressin (8-L-arginine vasopressin) of the posterior pituitary gland. Vasopressin is a hormone involved in water conservation, regulating the permeability of the renal collecting ducts to water (at concentrations of 0.9 to 6.5 pmol per liter). In response to hypotension, endogenous vasopressin plasma concentrations increase and, at higher concentrations (9 to 187 pmol per liter), vasopressin exhibits vasoconstrictor effects (Landry 2001). However, after prolonged hypotension, plasma levels of endogenous vasopressin decrease, suggesting that there is a depletion of neurohypophyseal vasopressin.

Vasopressin has been marketed as a therapeutic agent for nearly a century. In 1928, Parke-Davis introduced natural vasopressin, an extract of the bovine posterior pituitary, into the US market and obtained the registered trade name Pitressin®. In 1941, Pitressin® Tannate Oil (NDA 3402) by subcutaneous or intramuscular administration was approved for the management of central diabetes insipidus. In 1984, Parke-Davis submitted NDA 19286, synthetic Pitressin® intravenous administration for “acute gastrointestinal bleeding;” however, Parke-Davis withdrew NDA 19286 in 1984. NDA 3402 was also withdrawn in 1998 for reasons other than safety or effectiveness (source: clinical pharmacology review).

Pitressin® administered intramuscularly or subcutaneously is approved for prevention and treatment of postoperative abdominal distention in abdominal roentgenography to dispel interfering gas shadows, and in central diabetes insipidus. However, *intravenous* Pitressin® is marketed and unapproved and has been used off-label for cardiopulmonary resuscitation and treatment of gastrointestinal hemorrhage and vasodilatory shock.

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).” In order to submit an application for approval of vasopressin, the sponsor 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.”

The currently marketed formulation contains a (b) (4) overage of the active ingredient (formulated at (b) (4) U/mL and labeled at 20 U/mL) to conform to the USP monograph for Vasopressin Injection that requires the drug product potency to be between 90.0% and 110.0%. The overage was added to compensate for the degradation of the drug product; however, the applicant was advised by FDA during a pre-NDA meeting (October 17, 2011) to manufacture “no-overage” registration batches to support filing of the NDA.

### 3. CMC/Biopharmaceutics

The CMC reviewer, Dr. Soldatova, concluded that NDA 204-485 “cannot be approved in its current form,” because of deficiencies in the drug substance and drug product deficiencies summarized in the 24-item Information Request letter (March 7, 2013). In addition, there are insufficient stability data for primary stability batches for granting the expiration dating period.

There were no CMC recommendations for post-marketing commitments, agreements, and/or risk management steps.

- General product quality considerations

The drug substance, vasopressin monoacetate, is a white powder. The structural formula is  $C_{46}H_{65}N_{15}O_{12}S_2$ . Of note, the proposed specification for vasopressin is not sufficient for release of drug substance.

Vasopressin is manufactured by (b) (4). Standard specifications for a parenteral dosage form have been proposed. However, the release and shelf-life specifications are different from each other, and different from those provided in the USP Monograph for Vasopressin Injection (except for pH limit at shelf-life); these include pH, assay, impurities and chlorobutanol content. In addition, the shelf-life limits for some impurities are very high.

The sponsor is referencing (b) (4) DMF (b) (4) for information on the drug substance. According to the CMC review, the original DMF (b) (4) was found to be inadequate. The current status of DMF (b) (4) is adequate with Information Request (May 22, 2013), based on the response to the Deficiency Letter.

The drug product formulation is vasopressin compounded in water with chlorobutanol added as a preservative and acetic acid added for pH adjustment. The marketed product using this formulation has historically included an overage of (b) (4) to maintain requirements of 20 Units/ml through its shelf-life. The drug product proposed in this NDA application is formulated without overages.

At a pH range of 3.4-3.6, the vasopressin acid salt is relatively stable in water. At pH below 3.4 and above 3.6, there is accelerated degradation of vasopressin.

The proposed vasopressin formulation may be diluted with 0.9% sodium chloride and used for 18 hours when stored at room temperature or up to 24 hours under refrigeration. However, vasopressin appears to be incompatible with 5% dextrose as diluent/intravenous solution.

- Facilities review/inspection

The Overall Acceptable Office of Compliance recommendation was made (January 8, 2013) for all manufacturing and testing sites for drug substance and drug product.

#### Biopharmaceutics:

The Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (Dr. Elsbeth Chikhale) recommended approval of NDA 204485.

The Applicant's request for a waiver of the requirement to provide evidence of in-vivo bioavailability does not apply, since the published literature is being used to satisfy the CFR requirement to characterize the bioavailability of the product.

The Biopharmaceutics review focused on the evaluation of differences between the proposed drug product formulation and the formulations of drug products used in the published literature. The four main publications supporting efficacy, safety and PK information were: Argenziano (1997); Malay (1999); Patel (2002); and Russell (2008). The Argenziano and Malay studies used Pitressin Injection, USP from Parke-Davis.

Dr. Chikhale felt that the proposed vasopressin concentration of 20 U/mL was comparable to the vasopressin concentration of the drug products used in the published literature. The differences in the amount of preservative in the drug products are not expected to affect vasopressin bioavailability via the intravenous route of administration. However, the pH of the formulation was felt to be critical since pH outside the 3.4-3.6 range will accelerate the degradation rate of vasopressin.

Dr. Chikhale has noted that the expiry date for the proposed drug product should be set, so that the vasopressin concentration will not drop below 18 U/mL, in order to be comparable to the drug products used in the published literature, and also in order to conform to the USP monograph for Vasopressin Injection.

Dr. Chikhale has also noted that vasopressin will be titrated to maintain blood pressure, so that vasopressin degradation can be compensated by a higher dose.

## **4. Nonclinical Pharmacology/Toxicology**

The nonclinical pharmacology/toxicology review team (Drs. Rama Dwivedi and Thomas Papoian) felt that the application was approvable.

The effects of AVP are mediated via V1a, V1b and V2 receptors. V1a effects include vasoconstriction, glycogenolysis, platelet aggregation and adrenocorticotrophic hormone

release. The cardiac effects of AVP result from coronary vasoconstriction, decreased coronary blood flow and altered vagal and sympathetic tone.

The no observed adverse effect level (NOAEL) was considered to be 0.76 µg/kg for AVP and 1.14 µg/kg for impurities in 4-week repeated dose study in rats.

In rats and dogs given AVP via IV bolus and infusion, peripheral vasoconstriction led to increased blood pressure and compensatory decrease in heart rate.

This reviewer could find no chronic (e.g. > 28 day) toxicology studies; however, this is not likely to be an issue for vasodilatory shock, an acute condition.

AVP did not show any genotoxic potential in mutagenicity and clastogenicity studies.

The sponsor did not conduct any formal carcinogenic or fertility impairment studies in animals.

Effects on reproductive health should be communicated in product labeling.

The Maternal Health team made labeling suggestions for Sections 8.1, Pregnancy, and 8.3, Nursing Mothers, and recommended deleting section 8.2, Labor and Delivery, as there is no known information on the effects of vasopressin on labor and delivery.

The review did not identify other notable issues.

## **5. Clinical Pharmacology**

Based on the consistent pressor effect of arginine vasopressin, the Office of Clinical Pharmacology recommended approval for catecholamine-refractory vasodilatory post-cardiotomy and septic shock in adults. There were no recommended Phase 4 requirements.

### Pharmacokinetic considerations:

The pharmacokinetics of vasopressin is infusion rate dependent and characterized by an increased clearance with increasing dose (Figure 1). At therapeutic dose levels, the pharmacokinetics of vasopressin patients with vasodilatory shock approaches dose proportionality. The apparent half-life is  $\leq 10$  minutes (beneficial in an intensive care unit setting).

Vasopressin is eliminated mainly by metabolism involving serine protease, peptidases and oxido-reductases; only about 7% of the dose is excreted unchanged in urine.

During constant infusions of 60-75 min at rates varying 35 fold, AVP attains an apparent steady-state within  $\leq 30$  min. The steady-state CL increases with increasing infusion rate suggesting nonlinear PK of AVP as shown in the below figures:

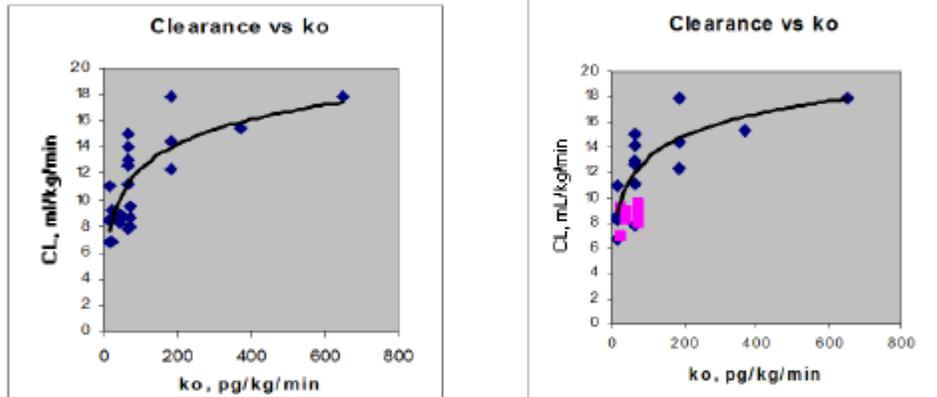


Figure 7a. Data of (37,38), solid trend line Figure 7b. Blue diamonds: data in males and females (37,38), purple rectangles are data females from (39,40). The solid line is a trend line

Figure 1. Steady-state clearance as a function of infusion rate (source: clinical pharmacology review)

The clearance of endogenous vasopressin is increased 4-fold in the second and third trimester of pregnancy without a change in the hormone plasma levels, indicating that the release rate from the pituitary is increased in proportion to the increased disposition. The increase in clearance of endogenous vasopressin due felt due to a spillover into blood of vasopressinase produced by the placenta. The clearance of exogenous vasopressin is also expected to increase during the second and third trimester of pregnancy.

There is no information about the effect of different degrees of renal or hepatic impairment on vasopressin pharmacokinetics and exposure. A report of vasopressin hemodynamic effects in 7 cirrhotic patients (Childs-Pugh C) showed prolonged pressor and HR effects compared with 6 matched controls. However, vasopressor will be titrated to BP effect with automatic dose adjustments.

An unresolved clinical pharmacology issue is that the diluents are unstated in most of the vasopressin publications. Arginine vasopressin has been shown to be stable in normal saline, but appears to be unstable when mixed with 5% dextrose. It might be more difficult to extrapolate dosing and BP effects in the published literature where there is a question of degradation of drug product.

Since vasopressin is titrated to effect, this is a concern where the need for titration occurs due to an inadequate response (perhaps related to degradation of drug product). In addition, one wonders whether vasopressin is efficacious at a lower starting dose (with normal saline).

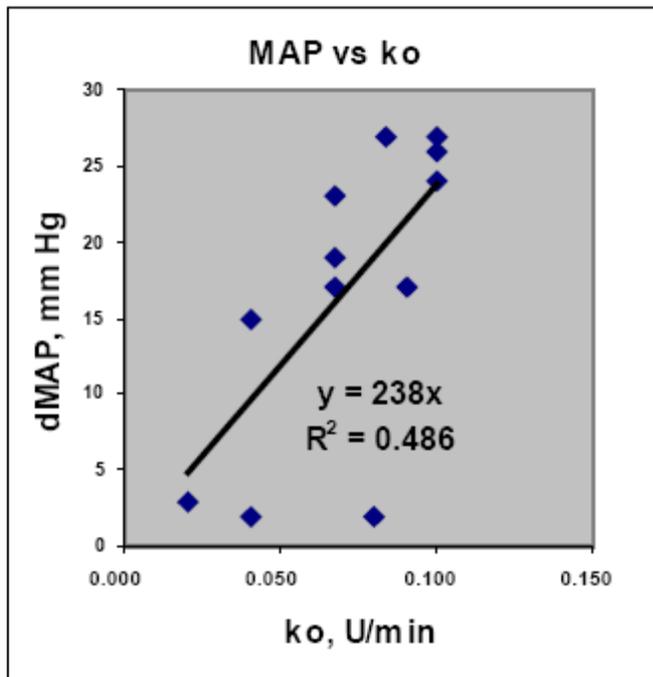
Pharmacodynamic considerations:

In patients with vasodilatory shock, effects on mean blood pressure begin within 15 minutes of infusion and there is no reported tachyphylaxis, unlike the effect observed in healthy subjects.

**Table 1. Vasopressin effects on MAP by population**

Subjects	Effect on MAP		
	Onset	Offset	Tachyphylaxis
Healthy	Within 5 min	During infusion	Yes
Shy-Drager	Within 5min	≤ 20 min after infusion stop	No
Vasodil. Shock	≤ 15 min	≤ 30 min after infusion stop	No

In the vasodilatory shock population, vasopressin consistently increased MAP and SVR, decreased the dose requirements of concomitant norepinephrine and tended to reduce heart rate and cardiac index. A trend for a dose-response relationship was observed by the clinical pharmacology reviewers regarding the effect of vasopressin on PVR, Map and NE dose requirements.



**Figure 2. Plot of % change from baseline in baseline-corrected mean arterial blood pressure vs. infusion rate (ko) in patients with vasodilatory shock or SIRS receiving AVP Pitressin (Parke-Davis) measured 2 hours after initiation of infusion (source: clinical pharmacology review, Figure 6). The plot of systemic vascular resistance was similar.**

Co-administration of other drugs with similar pharmacologic pathways could be expected to affect the response to vasopressin (or the concurrent drug). There is no information

characterizing the presence and extent of effect modification with catecholamines or drugs potentially inducing SIADH or diabetes insipidus.

There is no information exploring whether the pharmacokinetic or pharmacodynamic effects are modified with race, gender or advancing age.

The infusion rates of vasopressin in children were the adult doses normalized for body weight; only effects on MAP were consistently reported in the four pediatric studies.

No QT assessment was conducted. However, because vasopressin is being administered to patients with vasodilatory shock in intensive care units, patients will routinely receive continuous telemetry monitoring and close surveillance for the occurrence of arrhythmias. Cases of torsade de pointes have been reported after infusions of vasopressin, at higher than currently recommended exposures, in patients with alcoholic cirrhosis or hepatitis.

## **6. Product Quality Microbiology**

Dr. Erika Pfeiler recommended approval. There were no reported deficiencies or comments to the sponsor.

The drug substance is not sterile; however, the drug product is a sterile aqueous solution, containing the preservative chlorobutanol, and intended for multiple use. The microbiology reviewers felt that the container closure and preservative effectiveness studies were adequate to support microbiologic quality of the drug product.

The process validation studies, drug product specifications and stability program described were also adequate to support microbiologic quality of the drug product.

The microbiologic data support a post-dilution 24 hour hold time for the drug product at room temperature or under refrigeration.

There are no notable or outstanding issues.

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

In support of the proposed indication, the applicant provided 19 publications comprising a total of 1172 patients, of which 794 were treated with vasopressin. Seven of these studies were conducted in adult patients with septic shock, eight were conducted in adult patients with post-cardiotomy vasodilatory shock, three were conducted in pediatric patients with vasodilatory shock and one study was conducted in pediatric patients with vasodilatory shock.

**Table 2. Vasopressin prospective randomized studies**

Reference	Study design	N	Population	Vasopressin effects
Malay (1999)	DB, AVP + NE vs. placebo + NE	10	Septic shock (adult) MAP < 70 mm Hg on vasopressors	↑ MAP ↑SBP at 1 hour, ↑SVR, No Δ CI, HR, PAP
Patel (2012)	DB, AVP vs. NE , background pressors	24	Septic shock (adult) on vasopressors (baseline MAP 68 - 69 mm Hg)	↓ NE requirement ↑ Urine output ↑ Creatinine clearance BP maintained
Russell (2008)	DB, AVP vs. NE, primary endpoint all-cause mortality	778	Septic shock (adult) on vasopressors (baseline MAP 72 - 73 mm Hg)	↑ MAP ↓ HR, mean NE dose, No difference between groups in 28 day mortality
Dunser (2003)	Open, AVP + NE vs. NE	48	Adults vasodilatory shock (CV surgery or SIRS + or - sepsis) MAP < 70 mm Hg on NE	↑ MAP, CI, SVI, LVSWI, ↓ HR, NE requirement No Δ PAP, PCWP
Torgerson (2010)	Open, NE + AVP 0.033 or 0.067 U/min	50	Adults vasodilatory shock (sepsis, SIRS, cardiac surgery)	No Δ between groups in BP ↑ MAP , ↓ HR , arterial lactate, base deficit and NE requirement in both groups
Lauzier (2006)	Open, single-agent AVP vs. NE	23	Adults septic shock	↑ from baseline MAP and SVRI, ↓ HR, ↑ Creatinine clearance, ↓ SOFA scores vs. NE, NE required in 36% AVP patients
Hasija (2010)	DB, placebo-controlled	47	Adults undergoing CPB (+ or – ramipril or ramipril + prophylactic AVP)	No episodes of vasodilatory shock;post-CPB MAP normalized with prophylactic AVP but required ↑ dose of nitroglycerin.
Morales (2003)	DB, placebo-controlled	27	Adults on ACEI undergoing CPB	↓episodes of hypotension with prophylactic AVP
Papadopoulos (2010)	DB, saline control	50	Adults on preoperative ACEI undergoing CPB	Prophylactic AVP ↓incidence vasodilatory shock ↑MAP, CVP, SVR, EF No difference in PVR, PAP, HR
Argenziano (1997)	DB, AVP + NE vs. saline + NE	10	Adults LVAD placement and vasodilatory shock (MAP 60 mm Hg)	↑MAP and SVR ↓NE requirement No Δ CI, PAP
Choong (2009)	DB, background vasopressors + AVP or placebo	65	Pediatric patients vasodilatory shock (78% due to sepsis)	↑MAP 1 hour, No difference between groups: serum lactate, creatinine, urine output; 30-day mortality: 10 (30%) with AVP, 5 (16%) NE (p = NS)

DB= double-blind; AVP = arginine vasopressin; NE= norepinephrine; MAP= mean arterial blood pressure; SVR= systemic vascular resistance; NS=not significant; CI= cardiac index; HR = heart rate; PAP = pulmonary artery pressure; HR= heart rate; PCWP= pulmonary capillary wedge pressure; SVI= stroke volume index; CPB=cardiopulmonary bypass; LVSWI=left ventricular stroke work index; SOFA= Sepsis-related Organ Failure Assessment; ACEI=angiotensin converting-enzyme inhibitors.

In most of the studies in the above table, vasopressin was not used as a single-agent, but added to background therapy with one or more pressors. Titrations of background pressors, if they occurred, could have confounded blood pressure/outcome results. However, taken together, these studies support a temporal effect of vasopressin in increasing MAP and SVR in vasodilatory shock with hypotension despite fluids and catecholamine vasopressors (e.g., Malay, Argenziano, Dunser, Choong).

In some trials (e.g., Russell and Lauzier), mean baseline MAP measurements were above 70 mm Hg in the respective vasopressin groups and the relatively high baseline MAP might have affected results. For example, Lauzier observed a statistically significant increase from baseline in MAP beginning at 24 hours from the start of infusion, and not with earlier measurements at 1, 6 and 12 hours.

Measurements of pulmonary artery pressures support a lack of effect of vasopressin on the pulmonary vasculature (e.g., Malay, Papadopoulos, and Dunser)

Russell (VASST, Vasopressin and Septic Shock Trial), the largest study in the submission, was a randomized, double-blind study of adult patients with septic shock on fluids and low-dose norepinephrine (at least 5 µg/minute) to receive low-dose vasopressin (0.01 to 0.03 U/minute) or norepinephrine (5 to 15 µg/minute) in addition to open-label vasopressors. All infusions were titrated and tapered according to protocols to maintain a target BP. A computer-generated randomization list of variable permuted blocks were used for treatment allocation, which as stratified by center and severity of shock in the hour before randomization. The primary endpoint was all-cause mortality at 28 days after the start of infusion.

The study did not meet its primary endpoint. Exploratory subgroup analyses suggested that vasopressin was associated with improved survival in the subgroup with less severe shock. Other results included a decrease in heart rate and NE infusion rate in the group treated with vasopressin.

The medical and statistical reviewers found several limitations to the publications used as the sole basis to support efficacy, including lack of access to more detailed information concerning study design, conduct and results; differences in definitions, measurements and criteria for titration; lack of reporting of a single primary endpoint; potential for bias and selective reporting of results. I concur with their observations.

The statistical reviewer, Dr. Fanhui Kong, concluded that the clinical studies identified from the published literature seem to suggest that vasopressin may have an effect to increase blood pressure, measured by SBP, DBP, MAP, to treat or prevent hypotension due to perioperative vasodilatory shock and septic shock. However, although a large body of published literature is available, the publications inherit potential for bias and none of the studies meets the standard of “adequate and well controlled study” for conducting a confirmatory trial. Statistical issues are found in all of the studies and Dr. Kong felt that the results from the identified studies and

analyses are exploratory and do not provide confirmatory evidence to support the effectiveness of vasopressin.

While I concur with Dr. Kong's criticisms of the publications, I would consider the consistency of vasopressin's effect in raising MAP and SVR in the setting of catecholamine refractory vasodilatory shock, across numerous publications from different institutes and countries; while publication bias is a concern, there is a lack of publications refuting vasopressin's ability to raise blood pressure in this condition. In addition, preclinical data in several species and models are consistent with vasopressin's ability to raise BP.

The clinical reviewer, Dr. Fiszman, recommended approval of vasopressin as a second-line agent in the treatment of hypotension in vasodilatory shock (including postcardiotomy and septic shock), to be used in patients who remain hypotensive despite adequate fluid resuscitation and catecholamine administration. I would concur with Dr. Fiszman once the CMC deficiencies are resolved.

## **8. Safety**

Vasopressin has been marketed for over 98 years, in various formulations and routes of administration, including exposure to higher doses than those proposed for this indication. Thus, there is a fair amount of clinical and pharmacologic experience with vasopressin, which might pose some reassurance regarding adequacy of the safety database and characterization of safety profile.

Another consideration is that the targeted population, with vasodilatory shock and hypotension despite fluids and catecholamines, can develop adverse events and mortality due to the underlying condition. Even with a randomized, blinded study, these patients are usually on multiple concomitant medications, including other pressors and antibiotics that might confound attribution of safety results. For these reasons, it might be difficult to interpret whether signals are related to vasopressin, underlying disease, or concomitant therapy.

A total of 794 subjects were exposed to vasopressin IV infusion in 19 publications submitted with this application; while underestimating actual exposure over the decades of marketing, the number of subjects exposed should be adequate to characterize large or unusual effects for a therapy that is either acute or "subacute" (e.g., over days or weeks) but not chronic. One can also worry about underreporting of adverse events in the submitted published studies; however, the clinical reviewer also conducted an independent literature search, used data mining and requested an Office of Surveillance and Epidemiology review of pharmacovigilance data for serious adverse events. If there were a large enough signal for a serious or unusual adverse event suspected to be caused by vasopressin therapy, this safety signal would have been likely to have been published some time over the 98 years of vasopressin use.

In her review, Dr. Fisman reported the most common adverse effects of vasopressin with the proposed therapeutic doses (below). At least some of these effects are consistent with: regional vasoconstriction (e.g., mesenteric, digital or skin ischemia) or retention of free water (hyponatremia). It should be noted that regional vasoconstriction can also occur with catecholamine vasopressors.

Dr. Fisman has also noted reports of decreased platelet counts after vasopressin treatment, perhaps related to the underlying condition or activation of platelet V<sub>1a</sub> receptors with platelet aggregation.

**Table 3. Common adverse events of vasopressin in vasodilatory shock (source: clinical review)**

Type of Adverse Effect	Adverse Effects
Cardiovascular	Decreased cardiac output
	Bradycardia
	Tachycardia
	Tachyarrhythmias
	Coronary ischemia
Gastrointestinal	Mesenteric ischemia
Dermatologic	Skin ischemic lesions
	Digital ischemia
Metabolic	Hyponatremia
	Increased bilirubin

Source: [Russell 2007](#).

Data-mining and a review of FAERS (FDA Adverse Event Report System) cases by the Division of Pharmacovigilance I and the clinical reviewer yielded Preferred Terms (PT) that were, for the most part, consistent with the condition being treated (e.g., hypotension, diabetes insipidus, cardiac arrest, pulse absent) or expected effects (e.g., bradycardia).

The data-mining search revealed a signal for rhabdomyolysis. This reviewer found four literature case reports of rhabdomyolysis in patients with liver disease and bleeding esophageal varices, who were given IV infusions of vasopressin and developed cutaneous necrosis and rhabdomyolysis (Moreno-Sanchez 1991), myalgia, muscle weakness and extremity skin mottling (Hino 1995), or skin mottling and painful extremities (Pierce 1993). It appears that the doses of vasopressin used were higher than the proposed dose range (e.g., 0.2 U/min).

Nonetheless, some precautionary information should be added to the package insert, perhaps in the overdose section.

Additional findings of note include:

- Safety in pediatric patients:

The sponsor submission included one prospective, randomized, double-blind study of vasodilatory shock (mixed etiologies, but mostly due to septic shock) in pediatric patients 4 to 14 years old (Choong 2009) who were randomized to receive low-dose vasopressin or placebo in addition to open-label vasoactive agents. The primary endpoint, time to vasoactive-free hemodynamic stability, was not met. There were 10 deaths (30%, N = 35) in the vasopressin group and 5 deaths (16%, N=34) in the placebo group (relative risk, 1.94; 95% CI 0.75 to 5.05; p = 0.24).

The reader is referred to Dr. Fiszman's clinical review (Table 10) for a listing of the 15 fatal cases in the Choong paper. The most common cause of death was refractory shock and multiple organ dysfunction. Patients with septic vasodilatory shock had a mortality rate of 18.5%, compared with a mortality rate of 33.3% among patients with vasodilatory shock due to nonseptic causes; this difference in mortality rate was not statistically significant. There was no statistically significant association between baseline vasopressin levels and mortality; between concurrent steroids and vasopressin use and mortality; and none of the deaths were attributed to the study drug upon review by the site investigator, the local Research Ethics Board and the DMSC.

In her paper, Choong concluded that "low-dose vasopressin did not demonstrate any beneficial effects in this pediatric trial. Although not statistically significant, there was a concerning trend toward increased mortality." Based on the Choong conclusion, the sponsor shifted from proposed labeling in postcardiotomy shock to a recommendation against use in pediatric patients and a waiver for pediatric studies based on the safety concern from the Choong paper. Please see the Pediatric section (below, Section 10) for further discussion.

- Cases of torsades de pointes (TdP):

Dr. Fiszman reported five literature cases of patients with alcoholic hepatitis and cirrhosis being treated for bleeding esophageal varices due to portal hypertension; TdP events were reported with high doses of vasopressin (> 0.5 U/min) given as intra-arterial or IV bolus or infusions, at least 5-fold higher than the highest recommended dose rate in this submission.

There have been no reports of TdP within the proposed dose range. In addition, patients with vasodilatory shock and hypotension are administered pressors in a monitored setting, under continuous telemetry; thus, any arrhythmias would be observed and treated expeditiously.

## **9. Advisory Committee Meeting**

This application was not presented to an Advisory Committee.

## 10. Pediatrics

This application and waiver requests were discussed at a Pediatric Review Committee (PeRC) meeting on May 8, 2013.

- On March 6, 2013, the sponsor requested a full Pediatric Waiver from the requirement for pediatric studies under Section 505 b (a) (4) (A). The justification for the waiver request was that “there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.” Granting this request, with consistent labeling, would likely lead to a recommendation against use in pediatric patients.
  - In support of their request, the sponsor 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. Therefore, the use of Pitressin in pediatric patients is not recommended.”
  - The sponsor also cited Choong (2009), which 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; the authors noted 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, the authors concluded that low-dose vasopressin did not demonstrate any benefits in pediatric vasodilatory shock.
- The reviewers requested a full Pediatric Waiver from the requirement for pediatric studies based on the infeasibility of conducting such as study, rather than the safety concern based on the adverse mortality trend in the Choong study. The labeling outcome would be that “safety and efficacy have not been demonstrated in pediatric patients.”

The following topics were discussed:

- The feasibility of conducting a trial in pediatric patients with vasodilatory shock. In the Choong study, screened a total of 512 potential patients in seven pediatric critical care units over about 5 years, of which 106 (21%) met eligibility criteria and 69 were enrolled.
- Whether the adverse mortality trend for vasopressin in the Choong publication was due to drug effect, underlying condition or chance.
- Current guidelines for vasopressin use in pediatric patients with vasodilatory shock (“The use of vasopressin...has been described in a number of case reports, yet

evidence to support this in pediatric sepsis, as well as safety data, are still lacking. Indeed, two randomized controlled trials showed no benefit in outcome with use of vasopressors in children. Interestingly, while vasopressin levels are reduced in adults with septic shock, such levels seem to vary extensively in children...”). The guidelines recommend considering vasopressin as a second-line therapy, in patients remaining hypotensive despite fluids and norepinephrine.

- Differences between pediatric and adult vasodilatory shock (e.g., different presentations and mortality rates).
- The effect of contraindicating vasopressin use and whether this would harm pediatric patients who remain hypotensive despite fluids/catecholamines.

The PeRC committee recommended granting a deferral, rather than a waiver, with a postmarketing requirement for the sponsor provides data (e.g., narratives/case reports/datasets) for the results of the pediatric studies including the Choong study.

This reviewer concurs. However, the ultimate outcome and labeling for pediatric patients remains an unresolved issue at this time. Depending on the future evidence, the Agency should also consider discussing regulatory and labeling options at a future Pediatric Advisory Committee meeting.

## 11. Other Relevant Regulatory Issues

The sponsor’s proposed proprietary name, (b) (4), was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA), because of phonetic similarity and overlapping product characteristics with the currently marketed product (b) (4). During an evaluation of the sponsor’s proposed name, DMEPA confirmed medication errors that resulted in serious outcomes, including death, as a result of the confusion between (b) (4). DMEPA considered (b) (4); DMEPA concluded (b) (4).

This reviewer concurs with their conclusion.

As of May 17, 2013, the sponsor submitted a new proposed trade name, (b) (4) which is currently under review by DMEPA.

## 12. Labeling

Physician labeling is being extensively revised by the review team. Sections being revised include: Dosing and administration Use in pregnancy; Clinical studies and Adverse events sections.

No Medication guide is required.

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

- Recommended Regulatory Action

I recommend a Complete Response (non approval) action because of unresolved CMC deficiencies. Upon resolution of CMC issues, I would recommend approval of vasopressin for increasing mean arterial blood pressure in vasodilatory shock, including septic shock and post-cardiotomy vasodilatory shock (vasoplegic syndrome) for use in patients who remain hypotensive despite fluids and catecholamine administration.

- Risk Benefit Assessment

The benefit of vasopressin therapy relies on its ability to increase blood pressure, consistently demonstrated in patients with vasodilatory shock who have been treated with fluids and catecholamine vasopressors. Increasing or maintaining blood pressure can be considered a benefit in maintaining tissue perfusion and organ function; several studies (e.g., Patel, Lauzier, Togerson) have suggested a decrease in serum lactate and increase in urine output and creatinine clearance, consistent with expected improvement in tissue perfusion and oxygenation. One might also avoid the consequences of untreated hypotension, including organ system failure and death, but these benefits have not been demonstrated in this application.

Main risks of vasopressin therapy, in the recommended dose range, appear to be related to its pharmacologic activity (e.g., reduced platelet count, vasoconstriction/ischemia of mesenteric system, digits, skin, etc.); one hopes that in the intensive care unit setting, providers will monitor for these risks and manage the patient accordingly.

I believe that my recommended regulatory action is consistent with the conclusions of the review team. While I concur with the statisticians regarding omissions and potential for bias in the published literature, I base my conclusion of benefit on the temporality and consistency of vasopressin's pressor effect, as observed in animal, clinical pharmacology and clinical studies.

- Recommendation for other Postmarketing Requirements and Commitments

As discussed with the Pediatric Review Committee, I concur with recommending a postmarketing requirement (PMR) for the sponsor to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in this submission.

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

/s/  
-----

SHARI L TARGUM  
06/13/2013

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 204-485  
Priority or Standard Standard

Submit Date(s) September 25, 2012  
Received Date(s) September 26, 2012  
PDUFA Goal Date July 26, 2013  
Division / Office Division of Cardiovascular and Renal Products

Reviewer Name(s) Mónica L. Fiszman, M.D., PhD  
Review Completion Date May 24, 2013

Established Name Vasopressin Injection, USP  
(Proposed) Trade Name Pitressin® Injection  
Therapeutic Class Vasoconstrictor, vasopressor  
Applicant JHP Pharmaceuticals, LLC

Formulation(s) Injection  
Dosing Regimen Intravenous Infusion  
Indication(s) Vasodilatory shock (including post-cardiotomy shock and septic shock)

Intended Population(s) Adults

Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>7</b>
1.1	Recommendation on Regulatory Action .....	7
1.2	Risk Benefit Assessment.....	7
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	8
1.4	Recommendations for Postmarket Requirements and Commitments .....	8
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>9</b>
2.1	Product Information .....	9
2.2	Tables of Currently Available Treatments for Proposed Indications .....	9
2.3	Availability of Proposed Active Ingredient in the United States .....	10
2.4	Important Safety Issues with Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	10
2.6	Other Relevant Background Information .....	10
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>10</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>11</b>
4.1	Chemistry Manufacturing and Controls .....	11
4.2	Clinical Microbiology.....	11
4.3	Preclinical Pharmacology/Toxicology .....	11
4.4	Clinical Pharmacology .....	12
4.4.1	Mechanism of Action.....	12
4.4.2	Pharmacodynamics.....	12
4.4.3	Pharmacokinetics.....	12
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>13</b>
5.1	Tables of Studies/Clinical Trials .....	13
5.2	Review Strategy .....	16
5.3	Discussion of Individual Studies/Clinical Trials.....	17
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>22</b>
6.1	Indication.....	22
6.1.1	Methods .....	22
6.1.2	Demographics.....	23
6.1.3	Subject Disposition .....	23
6.1.4	Analysis of Primary Endpoint(s).....	23
6.1.5	Analysis of Secondary Endpoints(s).....	25
6.1.6	Other Endpoints .....	26

6.1.7	Subpopulations .....	26
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ....	26
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	26
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>26</b>
7.1	Methods.....	26
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	27
7.2	Adequacy of Safety Assessments .....	27
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	27
7.2.2	Explorations for Dose Response.....	27
7.2.3	Special Animal and/or In Vitro Testing .....	27
7.2.4	Routine Clinical Testing .....	28
7.2.5	Metabolic, Clearance, and Interaction Workup .....	28
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	28
7.3	Major Safety Results .....	28
7.3.1	Deaths.....	31
7.3.2	Nonfatal Serious Adverse Events .....	33
7.3.3	Dropouts and/or Discontinuations .....	33
7.3.4	Significant Adverse Events .....	34
7.4	Supportive Safety Results .....	35
7.4.1	Common Adverse Events .....	35
7.4.2	Laboratory Findings .....	35
7.4.3	Vital Signs .....	36
7.4.4	Electrocardiograms (ECGs) .....	36
7.4.6	Immunogenicity.....	38
7.5	Other Safety Explorations.....	38
7.5.1	Dose Dependency for Adverse Events .....	38
7.6	Additional Safety Evaluations .....	39
7.6.1	Human Carcinogenicity.....	39
7.6.2	Human Reproduction and Pregnancy Data.....	39
7.6.3	Pediatrics and Assessment of Effects on Growth .....	39
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	40
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>40</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>46</b>
9.1	Literature Review/References .....	46
9.1.1	Vasodilatory Septic Shock (Adults) .....	46
9.1.2	Vasodilatory Postcardiotomy Shock (Adults).....	58
9.1.3	Vasodilatory Postcardiotomy Shock (Pediatric).....	70
9.1.4	Vasodilatory Septic Shock (Pediatric) .....	73
9.2	Labeling Recommendations .....	76
9.3	Advisory Committee Meeting.....	76

## Table of Tables

Table 1- Summary- Efficacy Studies .....	14
Table 2. Summary-Vasodilatory Septic Shock Studies (Adults) .....	14
Table 3-Summary- Postcardiotomy Shock Studies (Adults).....	15
Table 4-Summary- Pediatric Studies.....	16
Table 5- Hemodynamic Parameters (Malay 1999).....	24
Table 6-Hemodynamic Response (Argenziano 1997).....	25
Table 7-Common Adverse Events Reported in Adults (Russell 2007) .....	28
Table 8-Vasopressin Safety Profile in Children (Choong 2009) .....	29
Table 9- Sponsor Safety Database by SOC and PT (June 2001- April 30, 2012) .....	30
Table 10-Fatal Cases (Choong 2009) .....	32
Table 11-Serious Adverse Events-Vasopressin and Norepinephrine (Russell 2008)....	33
Table 12-Effects of Vasopressin on Bilirubin and Platelets (Dunser 2003) .....	36
Table 13- Bilirubin and Platelets (Luckner 2007).....	39
Table 14- Baseline characteristics of Patients with Ischemic Skin Lesions (Dunser 2003) .....	41
Table 15-FAERS Search Strategy .....	42
Table 16- Empirica Signal Search Strategy.....	42
Table 17- Total number of FAERS reports with a serious outcome .....	43
Table 18-Pediatric Cases with Serious Outcome .....	43
Table 19- Adult Cases with Serious Outcome.....	44
Table 20- Vasopressin-Hemodynamic Effects (Patel 2002).....	51
Table 21- Vasopressin effects on hemodynamics and NE requirements (Argenziano 1999).....	62
Table 22-Cardiac parameters and vasopressor doses of study patients (Dunser 2002)64	
Table 23- Prophylactic effect of Vasopressin on Vasodilatory Shock post-CPB (Hasija 2010).....	66
Table 24- Pediatric Patients Profile (Rosenzweig, 1999) .....	72
Table 25- Baseline characteristics of pediatric patients (Choong 2009).....	75

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

## Table of Figures

Figure 1- Chemical structure .....	9
Figure 2-MAP during long-term AVP infusion (Russell 2008).....	24
Figure 3- 2012 Data Mining results- PTs with EB05 scores >2 .....	45
Figure 4-Vasopressin on 28-day and 90-day mortality (Russell 2008) .....	49

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

## LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin converting enzyme inhibition
AVP	Arginine-Vasopressin or Vasopressin
AE	Adverse events
BP	Blood Pressure
CA	Catecholamines
CABG	Coronary Artery Bypass Graft
CI	Cardiac Index
CL	Chloride
CO	Cardiac output
CPB	Cardio-pulmonary Bypass
CVP	Central Venous Pressure
DA	Dopamine
DBP	Diastolic Blood Pressure
EF	Ejection Fraction
EPI	Epinephrine
GI	Gastrointestinal
HR	Heart Rate
H	Hour
ICU	Intensive Care Unit
IV	Intravenous
L	Liter
LVAD	Left ventricular assist device
LVSWI	Left ventricular stroke work index
MAP	Mean Arterial Pressure
Min	Minutes
MPAP	Mean Pulmonary Artery pressure
NE	Norepinephrine
OHT	Orthotopic heart transplantation
OL	Open-label
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PHE	Phenylephrine
PVR	Pulmonary vascular resistance
RVSWI	Right ventricular stroke work index
SBP	Systolic Blood Pressure
SIRS	Systemic Inflammatory Response Syndrome
SVI	Stroke Volume Index
SVR	Systemic Vascular Resistance
TA	Tachyarrhythmia
U	Units

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends approval of vasopressin in the treatment of hypotension in vasodilatory shock (including post-cardiotomy and septic shock). This reviewer does not recommend the use of vasopressin as first-line agent. Treatment with vasopressin is recommended only in conditions unresponsive to adequate fluid resuscitation and with a decreased response to catecholamines (CA).

### 1.2 Risk Benefit Assessment

Preclinical *in vitro* and *in vivo* pharmacology studies have shown that vasopressin (AVP) activates V1 receptors in blood vessels and raises systolic and mean arterial blood pressure (SBP and MAP). Evidence from clinical studies supports the conclusion that AVP raises blood pressure (BP).

Intravenous (IV) AVP infusion has a rapid onset of action, can be titrated fast toward a goal BP, has a short lasting effect (minutes), and can be weaned off from systemic circulation rapidly. These pharmacokinetics features make AVP ideal for emergency therapy.

Risks of hypotension are related to decreased perfusion and oxygen delivery to vital organs (kidney, brain and heart) and consequently to organ damage. In acute hypotensive states, vasopressors are required to achieve a minimal perfusion pressure and maintain adequate flow to vital organs.

An increase in BP in vasodilatory shock can be considered a benefit. According to current sepsis management guidelines, norepinephrine (NE) is the first choice vasopressor recommended to treat vasodilatory septic shock, in order to maintain a MAP  $\geq$  65 mmHg<sup>1</sup>.

Development of adrenergic hyposensitivity with loss of CA vasopressor effects (CA-resistant/refractory vasodilatory shock), is a complication of concern in shock and it is considered a risk. Clinical data show consistently that AVP is a potent vasopressor under this condition. When patients do not respond to fluid resuscitation and vasopressor amines, treatment with AVP can be considered a benefit. However, there is no evidence of benefit with AVP given within the first 12 h of shock as a single agent (Lauzier 2006).

In severe CA-resistant vasodilatory shock, patients are treated with high doses of NE, which may increase the risk of toxicity due to extreme activation of  $\alpha$  and  $\beta$

---

1 Dellinger RP et al., Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care med. 2013 39: 165-228.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

adrenoceptors<sup>2</sup>. AVP decreases NE levels needed in CA-resistant vasodilatory shock patients (Argenziano 1997, Patel 2002, Russell 2008, Torgersen 2010). From the available information it cannot be concluded that sparing NE use is a benefit, or whether AVP use is safer than NE use. AVP adverse events profile is similar to that of other vasoconstrictors ( $\alpha$ 1 adrenoceptor agonists) and includes: distal limb ischemia, ischemic skin lesions and mesenteric ischemia. These adverse events have been reported with low AVP doses (0.01- 0.03 U/min) as well as with NE (Russell 2008). Conclusions about safety are limited since all study subjects were treated with background vasopressor medication.

In the pediatric studies, AVP increased SBP; three retrospective studies and one double blind placebo-controlled trial were submitted to the NDA. Information concerning safety in children is limited; a mortality trend was reported in one of the studies (Choong 2009). A further review of fatal cases and serious adverse events could help to the understanding of AVP safety profile.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None

### **1.4 Recommendations for Postmarket Requirements and Commitments**

The proposed pediatric claim in the original NDA was for post-cardiotomy vasodilatory shock. The sponsor revised the pediatric waiver request and on March 6, 2013 requested a full pediatric waiver to say that “Pitressin is not recommended in pediatric patients with post-cardiotomy vasodilatory shock or septic shock.”

On May 8, 2013 the PeRC subcommittee discussed the request for full waiver and recommended that the division disagree with the requested full waiver of pediatric studies, and to craft a PMR to request the collected data from the academic investigators to meet this request. The sponsor could fulfill the PREA PMR by submitting the data from the four studies conducted in children: the randomized, double blind controlled study (Choong 2009), and the 3 retrospective studies (Lechner 2007, Rosenzweig 1999, Alten 2012).

---

<sup>2</sup> Adverse effects expected with NE and not seen with AVP: Pulmonary hypertension, increased myocardial oxygen demand, hyperglycemia and lactate increase.

## 2 Introduction and Regulatory Background

AVP has been used off-label for decades as a vasopressor. Pitressin tannate, NDA 003402, an AVP formulation manufactured by Parke-Davis, was discontinued. AVP is approved in abdominal roentgenography, for prevention and treatment of postoperative abdominal distention to dispel interfering gas shadows, and in diabetes insipidus.

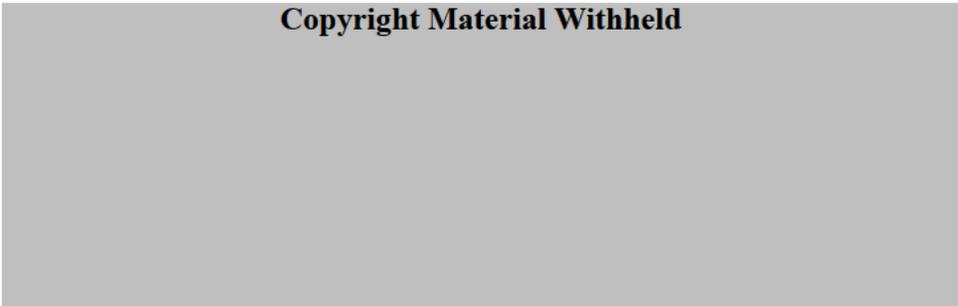
In June 2006, the FDA announced a new drug safety initiative to remove unapproved drugs from the market. To follow this initiative the sponsor met with the Agency in 2011 (see section 2.5) and submitted this application for AVP.

### 2.1 Product Information

AVP is synthesized in the hypothalamus via a polypeptide precursor that includes AVP, neurophysin, and copeptin and released in conditions such as hyperosmolality, hypotension and hypovolemia. After preliminary processing and folding, the precursor is packaged into neurosecretory vesicles, where it is transported down the axon, further processed to AVP, and stored in neurosecretory vesicles in the neurohypophysis until released by exocytosis into peripheral blood.

**Figure 1- Chemical structure**

Copyright Material Withheld



Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

AVP Molecular Weight: 1084.23

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Vasopressors commonly used to treat vasodilatory shock in the USA<sup>1</sup> include:

Phenylephrine (PHE): for increasing BP in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.

Norepinephrine (NE): for BP control in certain acute hypotensive states (e.g., pheochromocytectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

infarction, septicemia, blood transfusion, and drug reactions) and as an adjunct in the treatment of cardiac arrest and profound hypotension.

Dopamine (DA): for correction of hemodynamic imbalances presenting the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Epinephrine (EPI): although not approved to treat vasodilatory shock, it is one of the pressor amines used for this indication. EPI is indicated for the emergency treatment of allergic reactions (Type 1), including anaphylaxis and induction and maintenance of mydriasis during intraocular surgery.

### **2.3 Availability of Proposed Active Ingredient in the United States**

AVP has been commercialized for decades and the ingredients are available in the United States.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

Safety issues expected with vasopressor/vasoconstrictors are those described with  $\alpha_1$  adrenoceptor agonists such as metoxamine (discontinued) and NE and include: hypertension, local necrosis in the injection site, cardiac arrhythmias, pulmonary hypertension, bradycardia, gangrene of extremities and mesenteric ischemia. (<http://dailymed.nlm.nih.gov>).

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A Pre-IND (PIND 112944) meeting was held on October 17, 2011 to discuss the submission of an NDA under Section 505(b) (2) of the Federal Food, Drug and Cosmetic Act. FDA stated that it is possible to approve AVP without further outcome studies for increasing systemic arterial BP in certain acute hypotensive states and that increasing BP in shock can be interpreted to be desirable and so may serve as a basis for approval.

### **2.6 Other Relevant Background Information**

Off-label uses of AVP are: control of acute variceal hemorrhage and cardiopulmonary resuscitation; doses used are > 0.5 U/min (5 to 20 times higher than the proposed doses).

## **3 Ethics and Good Clinical Practices**

This was a literature-based application. The results of the published studies in this submission were collected long time ago and were conducted in several study sites

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

located in different countries. For these reasons this reviewer had no access to raw data, cannot conduct site inspections, and cannot conclude about integrity of an individual trial. There are no financial disclosures to review.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Lyudmila Soldatova, Ph.D., CMC reviewer, is not recommending approval of NDA 204-485 for Vasopressin Injection, in its current form from the CMC standpoint.

The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) deficiencies, and drug substance and drug product deficiencies summarized in the IR Letter dated 07-Mar-2013.

### **4.2 Clinical Microbiology**

Erika Pfeiler, Ph.D., Microbiology reviewer reviewed the sponsor's product quality microbiology and recommended approval.

Her conclusions were as follows:

It is a sterile aqueous solution for intravenous injection, packaged in a multi-use vial. It is (b) (4) The drug product contains the antimicrobial preservative chlorobutanol, and has an in-use period of 28 days. Following dilution in 0.9% saline, the drug product may be held for up to 18 hs at room temperature or up to 24 hs under refrigeration.

### **4.3 Preclinical Pharmacology/Toxicology**

Rama Dwivedi, PhD, reviewed the sponsor's pharmacology/toxicology submission and recommended approval.

His conclusions were as follows:

Increased systemic BP due to increased systemic vascular resistance (SVR) and a compensatory decrease in heart rate (HR) are the effects of AVP treatment in rats and dogs given IV bolus and IV infusion.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

A 14-day dose range study and 28-day repeated dose toxicity study in Sprague-Dawley rats, bacterial mutagenesis (Ames) and CHO chromosome aberration assays were conducted by the Sponsor for safety assessment of AVP and AVP degradation products (b) (4) to evaluate the toxic and mutagenic potential of AVP. No relevant toxicities were reported in the 28-day repeated dose toxicity study in rats. AVP did not show any genotoxic potential in mutagenicity and clastogenicity studies.

The Sponsor did not conduct any formal carcinogenicity or fertility impairment studies in animals to evaluate the effects of AVP, however, studies from published literature have shown that high doses of AVP might have adverse effects on reproductive function, fetal growth and development, and therefore, there may be a potential risk to the developing embryo and fetus.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Physiological actions of AVP include reduction of water excretion by promoting concentration of urine and contraction of smooth muscle in blood vessels and gastrointestinal (GI) tract. In addition, AVP potentiates adrenocorticotrophic hormone (ACTH) release by the corticotropin-releasing factor. Effects on vascular and gastrointestinal smooth muscle are mediated by V1a or V1b receptors coupled to phospholipase C.

### 4.4.2 Pharmacodynamics

AVP is a vasopressor in hypotensive states such as CA-resistant vasodilatory shock, a condition with low plasma AVP levels<sup>3</sup>. In doses ranging from 0.01 to 1 U/min AVP produced a rapid elevation of MAP, decreased HR and cardiac output (CO) and increased urine output.

### 4.4.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 U/min) the clearance of AVP is approaching dose independency and ranges between 9 and 25 mL/min/kg in patients with vasodilatory shock. The apparent t<sub>1/2</sub> of AVP at these levels is ≤10 min. AVP is predominantly metabolized and only about 65% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of AVP is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave AVP at

---

<sup>3</sup> Dunser MW, Wenzel V, Mayr AJ, Hasibeder, WR. Management of Vasodilatory Shock Defining the Role of Arginine Vasopressin. *Drugs* 2003, 63: 237-256.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Urinary concentrations increased linearly with dose and plasma concentration increased nearly linearly. AVP is metabolized by vasopressinase, a potent peptidase. The levels of vasopressinase are elevated up to 4-fold during pregnancy resulting in increased clearance of AVP

## **5 Sources of Clinical Data**

The source of clinical data was the published literature provided by the sponsor.

### **5.1 Tables of Studies/Clinical Trials**

To support efficacy, the sponsor submitted 7 studies conducted in adult vasodilatory septic shock patients and 1 study in pediatric subjects (majority septic shock patients), 8 studies conducted in post-cardiotomy adult patients and 3 studies in post-cardiotomy pediatric patients. These 19 publications included a total of 1,172 patients, of which 794 were treated with AVP.

**Table 1- Summary- Efficacy Studies**

No. of studies presented	Diagnoses	Patient population
7	Vasodilatory Septic shock	983 total, 551 received AVP to increase BP
8	3 Elective cardiac surgery	Total 124 patients 53 received AVP low dose for prophylaxis in shock
	5 Postcardiotomy shock	111 received AVP to increase BP
1	Majority with vasodilatory septic shock	65 (total) pediatric patient 4-14 years of age , 33 received AVP to increase BP
3	Vasodilatory postcardiotomy shock	28 pediatric patients (neonates to 15 years of age) treated with AVP 19 patients undergoing cardiac surgery AVP was given as a prophylactic agent

**Table 2. Summary-Vasodilatory Septic Shock Studies (Adults)**

Reference	Study type	n	AVP dose/time	Primary endpoint /variables
Malay 1999	Prospective, double-blind, randomized, placebo-controlled	Tot= 10 AVP= 5 NE= 5	0.04 U/min Placebo 1-24 h	<b>Arterial BP</b> ↑MAP, ↑SBP, ↑SVR, ↓CI
Patel 2002	Randomized, double-blind controlled	Tot=24 AVP=13 NE=11	0.01-0.08 U/min 4h infusion	<b>NE requirements (↓)</b> ↑Urine output, ↑creatinine clearance
Russell 2008	Multi-center, randomized, double-blind, stratified by severity	Tot:778 AVP=396 NE= 382	0.01 to 0.03 U/min 5 to 15 µg/min NE 90 days	<b>Death from any cause 28 days after (Failed)</b> ↑MAP, AEs
Dunser 2003	Prospective randomized controlled	Tot= 48 AVP= 24 NE= 24	AVP + NE 0.067 U/min NE 48 h	<b>Difference in hemodynamics between AVP and NE groups</b> ↑MAP, ↓HR No change: SVR MAP ↑ is > in AVP group
Torgersen 2010	Prospective randomized controlled open-label	Tot= 50 Dose 1= 25 Dose 2=25	0.067 U/min 0.033 U/min	<b>Difference in the hemodynamic effect of two AVP doses (no difference)</b>

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

				↑SVRI ↓NE requirements
Lauzier 2006	Randomized controlled open-label	Tot= 23 AVP= 13 NE= 10	AVP (1 <sup>st</sup> 12 h shock) 0.04-0.20 U/min 48 h infusion	↑MAP and SVRI ↓ CI (transient) ↑creatinine clearance
Holmes2001	Retrospective	Tot and AVP= 50	Average dose 0.05 U/min (0.01-0.6 U/min) 2h, 4h, 24h, 48h	↑MAP, ↓CI, ↓mean pressor dosage ↑urine output

**Table 3-Summary- Postcardiotomy Shock Studies (Adults)**

Reference	Study type	n	AVP dose/duration	Endpoint/Variable
Hasija, 2010 <sup>#</sup>	Prospective, randomized, double-blinded, placebo controlled single-center	Tot= 47 AVP= 15	AVP 0.03 U/min	Efficacy of prophylactic AVP infusion AVP prevented hypotension post-CPB Saline did not
Morales 2003 <sup>#</sup>	Randomized placebo-controlled Double-blind	Tot= 27 AVP= 13	0.03 U/min 72 h	AVP before CPB Prophylactic of post-CPB hypotension
Papadopoulos 2010 <sup>#</sup>	Double-blind randomized placebo (saline)	Tot= 50 AVP= 25 Saline= 25	0.03 U/min 4 h	AVP before CPB Prophylactic of post-CPB shock
Argenziano 1997	Prospective randomized placebo-controlled blinded study	Tot= 10 AVP= 5 NS= 5	0.1 U/min 15 min infusion	↑MAP and SVR, ↓NE requirements
Argenziano 1999	Retrospective	Tot= 175 AVP= 20	0.1 U/min 1 and 2 hs	↑MAP, SVR, CVP ↓ CI and NE need
Dunser 2002	Retrospective	Tot=991 AVP=41	0.06 to 0.1 U/min 2 days	↓HR, ↑ SVR and MAP and LCSWI no change in CI
Morales 2000	Retrospective	Tot=102	0.09 U/min	↑MAP, SVR

		AVP=50	7 days	
Argenziano 1998	Prospective	145 total		<b>Incidence of vasodilatory shock in a general cardiac surgery population and predisposing factors</b>
	Retrospective	AVP= 40	0.1 U/min 1h to 6 days	↑MAP and SVR, ↓NE need

\* Prophylaxis with low dose of AVP (0.03 U/min)

**Table 4-Summary- Pediatric Studies**

Reference	Study type	n	AVP dose	Primary Endpoint/ Variable
Choong 2009 <sup>1</sup>	Multicenter randomized controlled	Tot=65 AVP=33	0.0005-0.002 U/kg/min	<b>time to vasoactive-free hemodynamic stability (Failed)</b>  ↑ MAP 1h postdose
Alten 2012	Retrospective	Tot=37 AVP=19	0.0003 U/kg/min	Hemodynamic and safety data from AVP and non AVP
Lechner 2007	Retrospective	AVP=17	0.0001 -0.001 U/kg/min	↑SBP and ↓vasopressor requirements
Rosenzweig 1999	Retrospective	AVP=11	0.0003-0.002 U/kg/min	↑SBP and DBP no change in pressor needs

<sup>1</sup> Majority were vasodilatory septic shock patients; other: postcardiotomy, toxic, unknown.

## 5.2 Review Strategy

This is a publication-based application and has the following limitations:

- 1- The reviewer did not have access to the study database, study protocols, informed consents, or study sites and other information available in clinical trials conducted for an NDA.
- 2- Studies were conducted in different countries and different settings. Therefore definitions and measurements varied. Definition of hypotension, normal SVR, vasodilatory shock, criteria for titration of AVP and background vasopressors therapy varied by study.
- 3- Criteria for safety measurements of interest (i.e., mesenteric ischemia, digital ischemia and skin lesions) may vary by study.
- 4- The largest septic shock study (Russell 2008 , VASST trial, n= 778), a randomized, double-blind, controlled study, did not meet its primary endpoint (28-day mortality).
- 5- The majority of the publications did not define a primary endpoint instead, reported the effect of AVP on hemodynamic measurements at baseline and posttreatment. These studies with multiple endpoints are considered exploratory. As a measure of effectiveness, statistical comparisons of hemodynamic measurements between baseline and post baseline or between AVP and comparator were considered acceptable.

The medical reviewer prioritized randomized, double-blind, controlled studies. However, data from randomized open-label controlled studies were also reviewed. Retrospective analyses were considered as supporting evidence of benefit and risk.

Concerning safety, this reviewer assumed that adverse events were underreported. Therefore, in addition to safety results from sponsor's submitted original studies, safety information from review articles were also considered as well as post marketing reports, and results of a consult to the office of the FDA Surveillance and Epidemiology.

### **5.3 Discussion of Individual Studies/Clinical Trials**

Because of the patients' conditions all studies (except for Argenziano 1997) were conducted with all subjects under background open-label vasopressor medication<sup>4</sup>.

#### **Vasodilatory Septic Shock (Adults)**

For this indication, sponsor submitted the following information:

- Three prospective randomized double-blind controlled studies, comparing AVP to NE:
  - One placebo-controlled study (it is not a real placebo it is an arm with saline + fixed dose of NE, Malay 1999 n=10)
  - Two active- controlled studies (NE was the active comparator) NE titrated to a target BP, Russell 2008 n=778 and Patel 2002 n=24).

---

<sup>4</sup> Given the risks, it would be unethical to leave hypotensive patients on placebo

- Three randomized open-label studies:
  - Two were active-controlled studies (NE was the active comparator), Dunser 2003 (n=48) tested one fixed AVP dose and Lauzier 2006 (n=23) titrated AVP to BP target value. Another study by Torgersen 2010 (n=50) compared two fixed AVP doses.
- One retrospective study (Holmes 2001), analyzed 50 septic shock patients who received AVP for up to 48 h.

### **Postcardiotomy vasodilatory shock (Adults).**

For this indication, sponsor submitted two different sets of information:

- Studies conducted in patients with vasodilatory shock developed after weaning from cardiopulmonary bypass (CPB) and resistant to CA.
  - 1 randomized placebo-controlled blinded study (Argenziano 1997, n= 10). AVP fixed dose (0.1 U/min) compared to normal saline.
  - 4 retrospective studies without comparator. (Argenziano 1998, 1999, Dunser 2002 and Morales 2000, Total n=151).
- Studies conducted in patients undergoing elective cardiovascular surgery. A perioperative infusion of a low dose (0.03 U/min) of AVP was given for prevention and management of vasodilatory vasoplegic syndrome, in patients under angiotensin-converting enzyme inhibitors (ACEI). The rationale behind this is that inhibition of ACE predisposes patients to vasodilatory hypotension after CPB.
  - 3 randomized, double-blind, placebo-controlled studies. 127 patients undergoing elective cardiovascular surgery receiving ACE inhibitors from 2 to 6 weeks prior to the surgery participated in the study and 53 received a fixed dose of AVP (0.03 U/min).
  - Despite these were well designed studies, the information reported could not be used to support the indication since the baseline characteristics of the population studied differ substantially from the intended to treat population. i.e., patients were under elective cardiac surgery and not in shock, not all subjects required pressors at the time study started, MAP was normal (> 70 mmHg) and SVR information was not provided.

### **Vasodilatory shock (Pediatric)**

One multicenter randomized, double-blind, controlled trial by Choong 2009 (n=65) conducted in vasodilatory shock patients. Approximately 75% of the participants were

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

patients with septic shock; the rest were postcardiotomy, toxic and shock of unknown causes.

Subjects were randomized to either AVP or placebo. Subjects in both arms were under open-label vasopressors.

The primary outcome, the median time to achieve hemodynamic stability, failed. A pressor response with AVP was achieved after the first hour postdose.

Three retrospective studies were submitted to the NDA. Subjects with postcardiotomy shock received AVP: 19 were treated with a fixed dose of 0.0003 U/Kg/min (Alten 2012), 17 received 0.0001-0.001 U/kg/min (Lechner 2007), 11 received 0.0003 to 0.002 U/kg/min (Rosenzweig 1999).

### **Summary findings of the supporting prospective randomized double-blind controlled studies**

#### **Argenziano 1997 (Adult)**

This is a single-center study in 10 patients undergoing left ventricular assist device (LVAD) placement for end-stage heart failure. Subjects included had a MAP  $\leq 70$  mm Hg after weaning from CPB, despite NE administration in excess of 8  $\mu\text{g}/\text{min}$ , and LVAD CI greater than 2.5 L/min/m<sup>2</sup>. Subjects were evenly randomized to blinded AVP or normal saline. The observational time was 15 min.

Baseline characteristics were a MAP of  $60 \pm 2$  mm Hg, a CI of  $2.9 \pm 0.1$  L/min/m<sup>2</sup>, and a high requirement for exogenous NE ( $19.7 \pm 5.4$   $\mu\text{g}/\text{min}$ ) to maintain BP. Despite administration of CA, SVR was decreased ( $828 \pm 70$  dyne-s/cm<sup>5</sup>), indicating vasodilatory shock.

AVP increased MAP and SVR over baseline values and the effect was statistically significant (see Table 6). NE requirements decreased but the change was not significant.

This is a study with minimal bias that demonstrates a pressor response with AVP in postcardiotomy patients with vasodilatory shock. The effect is compared with saline (without background vasopressor) after 15 min of observation. Drawbacks are the small sample size and the short observational time.

#### **Choong 2009 (Pediatric)**

This study was conducted in 7 Canadian Pediatric Critical Care Units, in children 4 to 14 years of age with vasodilatory shock. The primary outcome was time to vasoactive-free hemodynamic stability.

Sixty-five of 69 randomized children (94%) received study drug (33 received AVP and 32 received placebo). All subjects were under background vasopressors. The median dose of AVP used was 0.0011 U/kg/min (interquartile range [IQR] 0.0007–0.0018) or 0.04 U/min.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Cause of vasodilatory shock differed between arms. Placebo arm has a more homogenous population with 88 % of the participants with vasodilatory septic shock vs 68 % in the AVP group. The AVP group had 3 (8.6%) patients with postcardiotomy vasodilatory shock vs 0% in the placebo group, 14.3 % of the patients in the AVP group had vasodilatory shock from undetermined cause vs 8.8% in the placebo group. There was no significant difference in the primary outcome between the two study groups. There was a significant increase in MAP 1- hour after infusion of AVP compared to baseline that was statistically significantly different from placebo.

There were 10 (30%) deaths in the AVP group, compared with five deaths (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval [CI], 0.75–5.05; P = 0.24). The five deaths reported in the placebo group and 6 of the 10 in the AVP group were treatment failure (Table 10). The four other deaths in the AVP group were probably confounded by underlying conditions rather than AVP exposure. For example one of the deaths reported mesenteric ischemia, an expected AVP serious AE. However, patient had post-radiation enterocolitis (Table 10). Two patients in the AVP group had digital ischemia and none in the placebo group (Table 8).

#### **Malay 1999 (Adult)**

Ten patients > 18 years of age with vasodilatory septic shock admitted to the trauma ICU were randomized to receive either AVP 0.04 U/min (n=5) or placebo (n=5). Placebo was normal saline + vasopressors. Open-label vasopressors were NE, PHE and DA. These drugs were weaned and discontinued provided that the MAP remained more than 70 mm Hg. Hemodynamic parameters were recorded at baseline and at 1, 4, 8 and 24 h post-dose.

NE requirements varied widely between subjects within each group: mean 12 (0-25) for the placebo group and 6.8 (4-30) for the treated group. Baseline MAP was 66 mmHg in the placebo group and 64 mmHg in the AVP group.

AVP administration increased MAP, SBP and SVR (Table 5). No changes were reported in the placebo group. AVP did not decrease HR and CI in this study, two commonly reported effects with AVP.

Two patients under placebo died (1 patient at 8 h and the other at 18 h post-treatment) because of refractory hypotension despite receiving standard CA. There were no post-baseline changes in sodium, base deficit or creatinine in the study. Drawbacks are the small sample size and the short observational time.

#### **Patel 2002 (Adult)**

The primary objective of the study was to examine the vasopressor sparing effect of AVP while maintaining hemodynamic stability and adequate end-organ perfusion (urine output and creatinine clearance, gastric mucosal carbon dioxide tension, and electrocardiogram ST segment position were measured). Twenty four patients experiencing severe septic shock who required high-dose vasopressors despite adequate fluid resuscitation were randomized to NE (n=11) or AVP (n=13), and open-label vasopressor.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Infusion of AVP or NE was given in a double-blinded fashion for 4 h. Starting dose of AVP was 0.01 U/min and the highest tested was 0.08 U/min, NE starting dose was 2 µg/min and maximal dose was 16 µg/min. During the initial 60 min of this 4-h infusion protocol, the study drug was titrated (every 5–10 min), and the pre-study vasopressor agent (NE) was titrated down to keep MAP constant. All other medications were held constant. No patients were unblinded during the 4-h study period.

The primary endpoint was statistically significant. In the AVP group, the NE infusion decreased from 25.0 µg/min (20.0, 37.3 µg/min) pre-study to 5.3 µg/min (0, 8.0 µg/min;  $P < 0.001$ ) at 4 h while maintaining MAP. The median AVP infusion rate in this group was 0.06 U/min.

AVP infusion increased urine output and creatinine clearance from baseline at 4 h post-dose (both  $P < 0.05$ ).

The weaknesses of this study are the low sample size and the short duration of the study. Whether the primary endpoint is clinically meaningful remains an open question. There is no study conducted so far to answer the question whether decreasing NE dose represents a benefit. The reported increase in creatinine and urine output may not be clinically relevant, long term changes on kidney parameters were not evaluated. Drawbacks are the small sample size and the short observational time.

### **Russell 2008**

This was a multi-center study conducted in subjects older than 16 years of age with septic shock resistant to fluids and low-dose NE ( $< 5$  µg/min). This was the largest study in this NDA database ( $n=778$ ).

Patients with septic shock, receiving a minimum of 5 µg of NE /min were randomized to receive either AVP (0.01 to 0.03 U /min) or NE (5 to 15 µg/min) in addition to open-label vasopressors. The blinded AVP infusion was started at 0.01 U /min and titrated (every 10 min) to a maximum of 0.03 U /min, whereas the blinded NE infusion was started at 5 µg/ min and titrated to a maximum of 15 µg/min. Open-label vasopressors were titrated to maintain a constant target MAP (65 to 75 mmHg was recommended). The mean age of enrolled patients in both groups was about 60 years.

Patients were severely ill in both groups as indicated by the high NE requirements ( $20.7 \pm 18$  µg/min, NE group;  $20.7 \pm 22$ , AVP group) and lactate levels (3.5 mmol/L, in NE and AVP group). MAP at baseline was 73-72 mmHg for NE and AVP group respectively. No SVR data were reported.

The study, designed to compare the effect of AVP and NE, was a randomized double-blind study and therefore the chances of bias were very low. The study failed to demonstrate a difference in the primary endpoint: 28-days mortality i.e., no difference was found between mortality rate in NE vs AVP. However, a trend toward higher survival rate was reported for the AVP group (Figure 4). The fact that AVP survival rate

was similar to that of NE is reassuring. AVP increased MAP to the same extent as NE but in contrast to other studies it took days (not hours) to reach its maximum (Figure 2). MAP at baseline was relatively high (73-72 mmHg, NE and AVP group respectively) compared to other publications with same patient population.

As in many of the studies conducted with this type of patients there is some background therapy that affects the interpretation of results. For example, in this case the bedside nurse titrated open-label vasopressors to maintain a constant target MAP. Moreover, the attending ICU physician could modify the target BP of each patient. Open-label vasopressors were increased only if the target MAP was not reached on maximal study drug-infusion.

A previous study raised the possibility that AVP may increase the incidence of cardiac arrest<sup>5</sup>. In this study 8 cardiac arrests were reported in the NE groups whereas 3 were reported in the AVP group. Because of the limited information it is difficult to conclude whether these events were due to AVP or to the underlying condition. Reported digital ischemia and mesenteric ischemia are expected AEs with AVP (Table 11).

## 6 Review of Efficacy

### 6.1 Indication

The proposed indication is vasodilatory shock (including post-cardiotomy shock in adults and pediatric and septic shock in adults).

#### 6.1.1 Methods

The levels of evidence were as follows

1. Randomized double-blind controlled studies. (Malay 1999, Patel 2002, Russell 2008, adult septic shock; Argenziano 1997, Morales 2003, Hasija 2010, Papadopoulos 2010, adult postcardiotomy shock; Choong 2009 vasodilatory shock pediatric indication).
2. Randomized open label studies (Dunser 2003, Lauzier 2006, Torgensen 2010 septic shock indication)
3. Retrospective (Holmes 2011, adult septic shock; Argenziano 1998, 1999, Morales 2000, Dunser 2002 adult postcardiotomy shock; Rosenzweig 1999, Lechner 2007, Alten 2012, for pediatric postcardiotomy shock).

#### Study subjects

---

5 Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001;27:1416-21.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

1. With vasodilatory shock <sup>6</sup>
2. Unresponsive to fluid resuscitation <sup>6</sup>
3. Resistant to NE treatment <sup>6</sup>
  - a. Inclusion criteria concerning NE dose: < 5 µg/min, Russell, 2008; < 8 µg/min, Argenziano 1997; ≤14 µg/min, Dunser 2002; 15 µg/min, Argenziano 1999.
  - b. NE dose at study entry: 10-20 µg/min (considered mild to severe shock<sup>7</sup>)
4. Normal or high CO/CI.

### 6.1.2 Demographics

There were four distinct populations in the efficacy studies:

1. Vasodilatory septic shock adult patients (age range 50 to 70 years of age, 7 studies, 551 patients treated with AVP, 200 women and 328 men; Dunser 2003 did not provide gender information).
2. Vasodilatory postcardiotomy shock adult patients (mean age 50-55 years, 5 studies, 156 patients treated with AVP, 25 women and 86 men, one study by Morales 2000 did not specify gender).
3. Adult patients undergoing cardiac surgery without vasodilatory shock treated with ACE inhibitors (3 studies, 53 subjects received AVP, 90% were men)
4. Vasodilatory postcardiotomy and septic shock pediatric patients 80 patients received AVP (neonates to 14 years of age).

### 6.1.3 Subject Disposition

Discontinuation rates were not reported in these studies.

### 6.1.4 Analysis of Primary Endpoint(s)

#### **Prospective randomized double-blind controlled studies**

##### Blood pressure (BP)

The reported pressure parameter was almost always MAP. Increase in MAP was the most consistent finding throughout the studies.

A prospective randomized double-blind, placebo-controlled study (Malay 1999) conducted in 10 patients with vasodilatory CA-resistant septic shock. The goal was to assess AVP as a pressor agent and the primary endpoint was BP. As shown in Table 5 an AVP infusion increased SBP, MAP and SVR in a statistically significant manner over baseline values.

---

<sup>6</sup> Except for Hasija 2010, Morales 2003, Papadopoulos 2010

<sup>7</sup> Based on the published literature in adults a NE dose ≤ 5 µg/min is considered low; ≥ 15-20 µg/min high (severe shock); > 30/40 µg/min very high

**Table 5- Hemodynamic Parameters (Malay 1999)**

**Copyright Material Withheld**

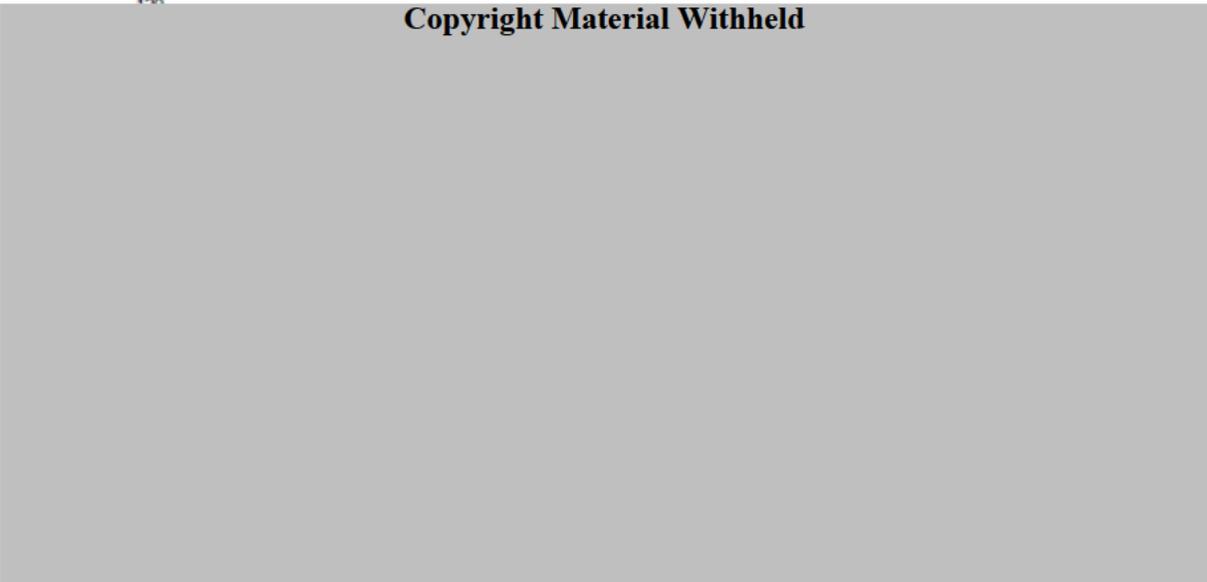


This is the only study submitted to this NDA with BP as a primary endpoint, authors do not specify if they referred to SBP or MAP or both. In all other studies, MAP and/or other hemodynamic parameters were routinely collected, analyzed and reported.

One example is the study by Russell 2008 (VASST trial), the largest trial submitted to this NDA, (n=778). This was a randomized double-blind, controlled multicenter study conducted in septic shock patients. Although the primary endpoint (28-day mortality vs NE) failed, low-dose AVP (0.01 to 0.03 U/min- infusion) increased MAP to the same extent as NE. It should be noted that in this study increase MAP effect developed very slowly (days instead of hours).

**Figure 2-MAP during long-term AVP infusion (Russell 2008)**

**Copyright Material Withheld**



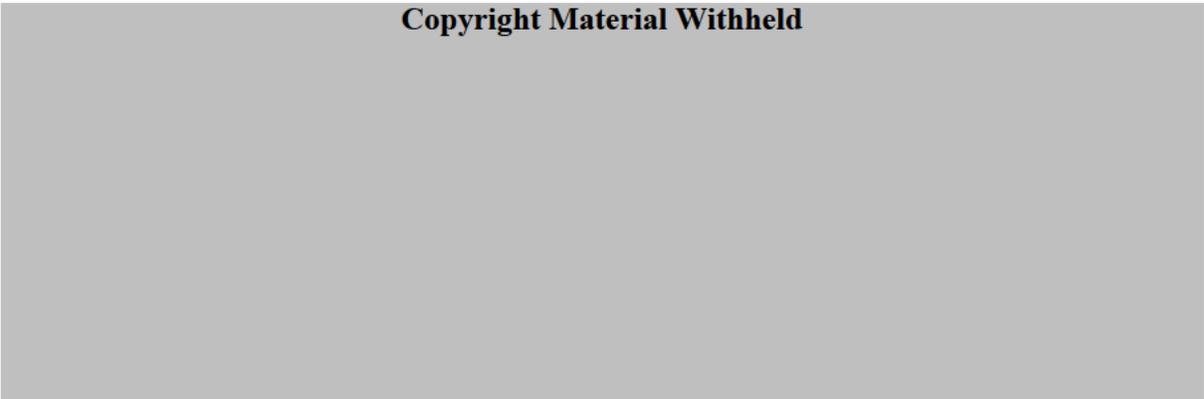
Source: Russell 2008, supplement.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Some studies did not mention any primary endpoint but reported hemodynamic measurements. An example is the prospective randomized double-blind placebo-controlled trial conducted in 10 patients with postcardiotomy vasodilatory shock after LVAD placement for end-stage heart failure (Argenziano 1997).

AVP increased MAP and SVR over baseline values and the effect was statistically significant (Table 6).

**Copyright Material Withheld**



Source: Argenziano 1997, Table 1.

#### Vasopressor sparing effect

One study had tested a vasopressor sparing effect as a primary endpoint (Patel 2002). A prospective, double-blind, randomized, controlled study was conducted in 24 patients experiencing severe septic shock who required high-dose vasopressors despite adequate fluid resuscitation. Arms were AVP (n=13) and NE (n=11) and open-label vasopressor in both arms.

Primary endpoint was statistically significant i.e., in the AVP group, the NE infusion decreased from 25.0 µg/min (20.0, 37.3 µg/min) pre-study to 5.3 µg/min (0, 8.0 µg/min; P <0.001) at 4 h while maintaining MAP. It is unclear whether sparing vasopressor amines represents a benefit.

#### 6.1.5 Analysis of Secondary Endpoints(s)

##### Systemic vascular resistance (SVR):

Septic shock studies: increase in SVR was reported by Malay 1999, Lauzier 2006 and Torgersen 2010. No effect on SVR was reported by Dunser 2003.

Postcardiotomy shock studies: Increase in SVR was reported by Argenziano 1998, 1999, Dunser 2002, Morales 2000.

##### Pressor requirements (sparing NE use)

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

As mentioned previously, Patel 2002 conducted a study in vasodilatory shock patients and the primary endpoint was reduction of vasopressor requirements.

The following studies reported reduced pressor requirements and confirm findings by Patel 2002:

Septic shock: Russell 2008, Torgersen 2010, Holmes 2001

Postcardiotomy shock: Argenziano 1997, 1998, 1999.

#### 6.1.6 Other Endpoints

##### Arterial lactate, base deficit and pH

Septic shock: arterial lactate and base deficit decreased while arterial pH increased with doses of 0.033 and 0.067 U/min AVP (Torgersen 2010).

Postbaseline arterial lactate decreased in Dunser 2003, a study with n=48 participant with vasodilatory shock.

##### Urine output

Urine output increase was reported in some of the studies. Although urine output could be a sign of better organ perfusion, the clinical meaningfulness of these findings is uncertain since no long term follow up in kidney function and viability (need for dialysis, transplant and creatinine clearance) was performed.

#### 6.1.7 Subpopulations

The submitted clinical trials did not distinguish between gender, age or race.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is an apparent linear dose response for MAP. Rapid onset peak effect and rapid offset supports a 15 min interval between dose increments. This confers ideal maneuverability for up-titration to BP effects and down titration, once effect is reached.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no evidence of tachyphylaxis or tolerance in this patient population.

## **7 Review of Safety**

### **7.1 Methods**

The sources of information provided by the sponsor were 1- literature search using PubMed, FDA.gov and ClinicalTrials.gov databases, 2-the comprehensive review of the

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

use of vasopressors for hypotensive shock conducted by the Cochrane Collaboration (Havel 2011). The search criteria employed for the Cochrane Report included a MEDLINE search (from 1966 to March 2010), EMBASE (from 1989 to March 2010), PASCAL BioMed (from 1996 to March 2010), and BIOSIS (1990 to March 2010).

The reviewer used the sponsor's literature reports, supplemented by several Pubmed searches (terms included "vasopressin;" vasopressin shock;" "vasopressin vasodilatory") and postmarketing reports searched by FAERS datamining.

As of April 25, 2012, the sponsor's database contained 76 cases (NDA Appendix 1, Listing of spontaneous adverse event reports June 2001-April 2012) where AVP was reported as a suspect drug; of these cases, 1 had a fatal outcome and is listed under Deaths (section 7.3.1).

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies were those submitted to the NDA and listed in summary tables (see section 5.1) and publications found in Pubmed by the medical reviewer.

### 7.2 Adequacy of Safety Assessments

#### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The sponsor submitted marketing data for the period of October 1, 2007 up to April 30, 2012. Total sales of Pitressin® were (b) (4) vials of the 1 mL (20 units/mL) presentation of Pitressin® injection and an additional (b) (4) vials sales were sold to a distribution partner (b) (4). From the 19 publications submitted to the NDA, 794 subjects were exposed to AVP using IV infusion in all cases. AVP has been marketed for many years and the numbers presented do not reflect the actual exposure, which should be higher.

#### 7.2.2 Explorations for Dose Response

Luckner 2007, performed a retrospective analysis for the 0.033 and 0.067 U/min AVP doses to search a dose-response relationship for hemodynamic and safety measurements.

#### 7.2.3 Special Animal and/or In Vitro Testing

A 14-day dose range study and 28-day repeated dose toxicity study in Sprague-Dawley rats were conducted by the Sponsor for safety assessment of AVP and AVP

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

degradation products (b) (4) to evaluate the toxic potential of AVP. No adverse effects were reported in 28-day repeated dose toxicity study in rats.

#### 7.2.4 Routine Clinical Testing

This information was not published.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

This information was not available

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not conducted. The only data available are serious AE reported with AVP vs NE in Russell 2008 (VASST study).

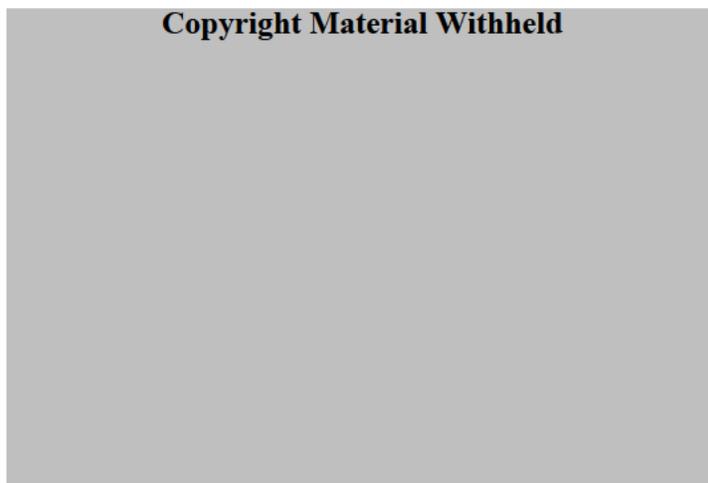
### 7.3 Major Safety Results

#### Adverse Events (Adults)

Table 7 illustrates the most common adverse effects of AVP with the proposed therapeutic doses; all these findings were confirmed in this submission material. In addition there are some reports of decrease in platelet counts after treatment with AVP.

**Table 7-Common Adverse Events Reported in Adults (Russell 2007)**

**Copyright Material Withheld**



Source: Russell 2007, Table 4

#### Adverse Events (Children)

Clinical Review  
 Mónica L. Fiszman, M.D., Ph.D.  
 NDA # 204-485  
 Vasopressin

A published safety database from 65 children (4 to 14 years of age) with vasodilatory shock treated with low doses (0.0005-0.002 U/kg/min) of AVP was reported (Choong 2009).

Two cases of digital ischemia and one serious event of cardiac arrest were reported in the AVP group and none in the placebo group (open-label vasopressors + saline).

**Table 8-Vasopressin Safety Profile in Children (Choong 2009)**

**TABLE 5. ADVERSE AND SERIOUS ADVERSE EVENTS**

	Vasopressin (n = 33)	Placebo (n = 32)	P Value
<b>Adverse event</b>			
Number of adverse events*, n (%); 95% CI	5 (15.2; 4.9–35.4)	1 (3.1; 0.1–17.4)	0.15
Digital ischemia	2		
Thrombocytopenia		1	
Bradycardia	1		
Hypotension	1		
Hypokalemia	1		
<b>Serious adverse event</b>			
Number of serious adverse events*, n (%); 95% CI	1; 3.0 (0.1–16.9)	2; 6.8 (0.8–22.6)	0.55
Cardiac arrest	1		
Gastrointestinal bleeding		1	
Right brachial artery clot		1	

Definition of abbreviation: CI = confidence interval.

\* Number of events per total number of patients.

Sponsor's Database

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Table 9 summarizes by System Organ Class (SOC) and Preferred Term (PT) those events which JHP or King reported to FDA between June 2001 and April 30, 2012. The most frequently reported cardiac and vascular disorders were bradycardia and hypertension respectively.

**Table 9- Sponsor Safety Database by SOC and PT (June 2001- April 30, 2012)**

System Organ Class (SOC)	Preferred Term	Frequency Term Reported	Frequency SOC Reported
Cardiac disorders	Bradycardia	5	14
	Cardiac arrest	4	
	Atrial fibrillation	1	
	Atrioventricular block	1	
	Cardiogenic shock	1	
	Supraventricular extrasystoles	1	
	Tachycardia	1	
Investigations	Alanine aminotransferase increased	1	11
	Blood alkaline phosphatase increased	1	
	Blood creatine phosphokinase increased	1	
	Blood pressure immeasurable	1	
	Blood sodium decreased	1	
	Hepatic enzyme abnormal	1	
	Oxygen saturation immeasurable	1	
	Pulse absent	1	
	Radial pulse abnormal	1	
	Renal function test abnormal	1	
	Troponin (increased)	1	
General disorders and administration site conditions	Drug ineffective	2	8
	Adverse drug reaction	1	
	Death**	1	
	Drug ineffective, unapproved indication	1	
	Drug withdrawal syndrome	1	
	Injection site erythema	1	
	Withdrawal syndrome	1	
Gastrointestinal disorders	Gastric dilatation	1	6
	Gastric disorder	1	
	Gastric haemorrhage	1	
	Gastrointestinal haemorrhage	1	
	Intestinal infarction	1	
	Small intestinal obstruction	1	

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

System Organ Class (SOC)	Preferred Term	Frequency Term Reported	Frequency SOC Reported
Vascular disorders	Hypertension	2	6
	Vasoconstriction	2	
	Hypotension	1	
	Haemorrhage	1	
Endocrine disorders	Diabetes insipidus	4	4
Renal and urinary disorders	Polyuria	2	3
	Oliguria	1	
Metabolism and nutrition disorders	Hypernatraemia	2	3
	Hypoglycaemia	1	
Surgical and medical procedures	Off label use	3	3
Injury, poisoning and procedural complications	Medication error	1	2
	Post procedural haemorrhage	1	
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	1	2
	Respiratory failure	1	
Skin and subcutaneous tissue disorders	Dermatitis bullous	1	2
	Skin necrosis	1	
Infections and infestations	Septic shock	1	1
Nervous system disorders	Grand mal convulsion	1	1

\*Multiple event term reported from each ICSR; includes both spontaneous and literature reports

\*\*This term was reported by King Pharmaceuticals from a literature report of a clinical trial in sepsis patients treated with drotrecogin alfa (activated) in which 28 of 50 patients who received vasopressin (not randomized) died. Individual patients and specifics of treatment were not identifiable, nor was it discernible whether treatment with vasopressin was considered a marker for severity of illness or specifically increased mortality; therefore only one ICSR was created for reporting to the FDA.

Source: Sponsor's Table 2.5.21

### 7.3.1 Deaths

#### Publications

##### **Adults**

In a case series by Holmes 2001, from the 50 vasodilatory septic shock patients, 8 patients survived to hospital discharge. The causes of death in the remaining 42 patients were: refractory shock (n = 20), withdrawal of care due to multiple system organ failure (n = 19 patients), late respiratory failure (n = 2) and cerebral edema due to underlying disease (n = 1).

In Lauzier 2006, 3 patients died during the study (2 in the AVP group and 1 in the NE group). In all cases death was attributed to refractory shock.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

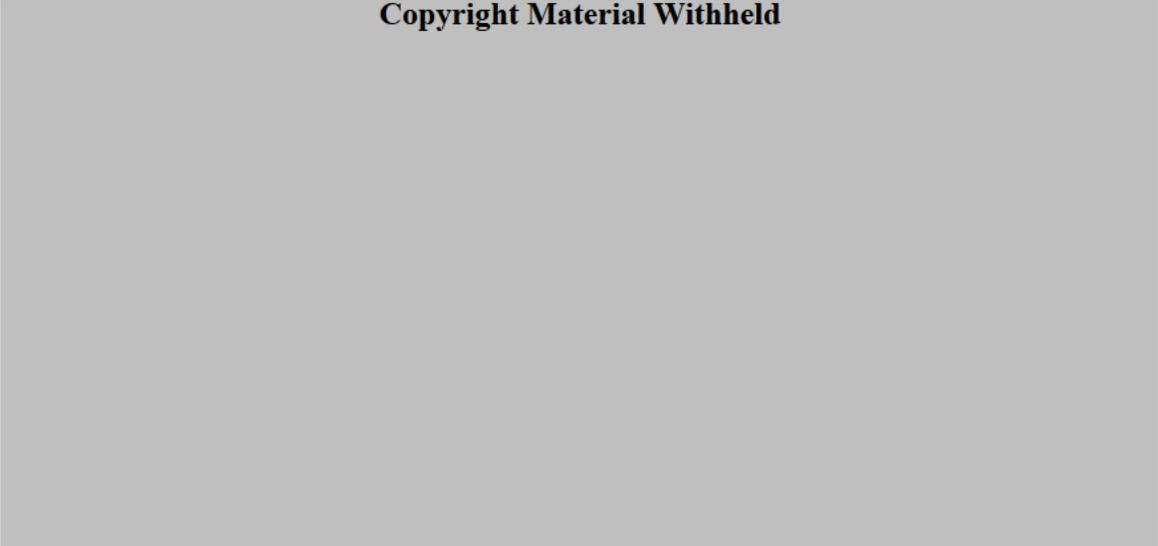
### **Pediatric**

In Lechner 2007, a retrospective study conducted in neonates, four patients died, 2 of them during AVP infusion. Both patients who died had hypoplastic left heart syndrome: one patient died 42 h post-operatively after prolonged hypoxemia and the second had cardiac arrest on post-operative Day 4, when AVP was almost weaned.

In Chong 2009, a randomized, double blind controlled study conducted in children (4 to 14 years of age) there were 10 (30%) deaths in the AVP group, compared with five deaths (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval [CI], 0.75– 5.05; P = 0.24). Most common cause of death in the two groups was treatment failure i.e, refractory shock and multisystem organ dysfunction syndrome. Some of the deaths in the AVP group are probably due to an underlying condition rather than AVP administration. However, the information is insufficient to draw any conclusion.

**Table 10-Fatal Cases (Choong 2009)**

**Copyright Material Withheld**



### Sponsor's database

There is one report of death in the sponsor database from the published literature<sup>8</sup>. A prospective, observational cohort study conducted in the intensive care units to identify potential risk factors for hospital mortality among patients with severe sepsis who were treated with drotrecogin  $\alpha$ . Patients who received at least a 48 h infusion of drotrecogin  $\alpha$  (activated) for severe sepsis with at least one unspecified organ derangement were eligible for investigation. Fifty of the 102 patients enrolled in this study received AVP, 28 died during their

---

8 Micek ST, Isakow W, Shannon W, Kollef MH Predictors of Hospital Mortality for Patients with Severe Sepsis Treated with Drotrecogin alfa (activated) Volume: 25, 2005 Pages: 26-34

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

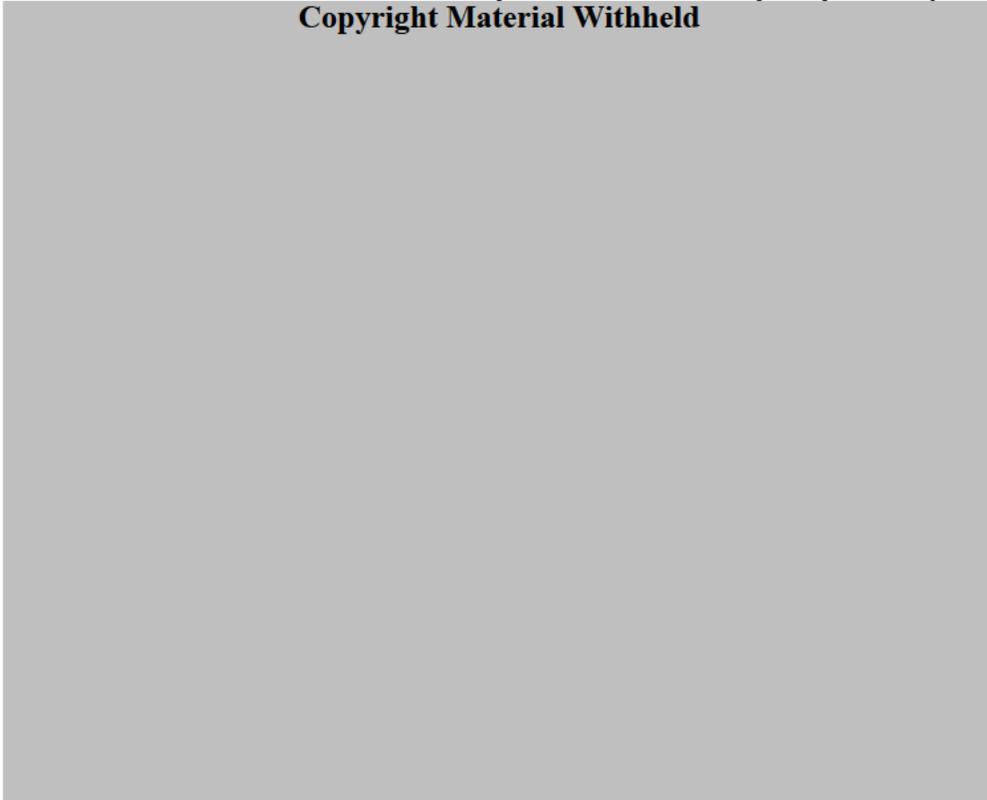
hospitalization. Cause of death was not confirmed. Specific details concerning the clinical course of individual patients were not presented.

Reviewer's comments: Since AVP has been used in severe hypotensive states including shock, some deaths related to underlying disease and unrelated to AVP may occur during treatment. In addition, AVP was not administered as a single agent. Therefore, comparison with background rates in matched populations would be important for detection of safety signals.

### 7.3.2 Nonfatal Serious Adverse Events

For clarity purposes this reviewer placed this serious AE information reported in adults in this section. Whether these events had fatal outcomes was not specified. In the VASST trial, more patients in the AVP group than in the NE group had digital ischemia; one patient in the AVP group required surgical intervention.

**Table 11-Serious Adverse Events-Vasopressin and Norepinephrine (Russell 2008)**  
Copyright Material Withheld



### 7.3.3 Dropouts and/or Discontinuations

Not reported in any study.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

#### 7.3.4 Significant Adverse Events

##### Torsade de pointes (TdP)

Five reports from the literature submitted in this NDA were all from studies in patients with alcoholic hepatitis and cirrhosis being treated for hematemesis due to portal hypertension. TdP events were reported with high doses of AVP (> 0.5 U/min) given intraarterial or in IV bolus (over 15 min) or given as high (0.5 U/min) dose IV infusions for the induction of vasoconstriction for the treatment of esophageal varices bleeding due to portal hypertension. The episodes of ventricular tachycardia (VT) or TdP were almost always preceded by bradycardia and premature ventricular contractions (PVC). The effect is seen with doses higher than those proposed for the vasodilatory shock indication and, in some cases, study drug was administered in bolus injection.

##### ST depression- Acute Coronary Syndrome (ACS)

In Lauzier 2006, one case of ACS occurred during the protocol in each group (AVP and NE), with concomitant increase in troponin I. The patient under AVP had no cardiovascular disease prior to admission; an angiography performed during infusion of AVP at 0.2 U/min revealed an occlusion of a small marginal artery. ECG changes (ST segment depression in lateral precordial leads) subsequently disappeared after tapering the AVP infusion to 0.04 U/min. None of these patients developed Q waves and creatine kinase levels remained normal.

##### Heart rate (HR):

AVP induced a decrease in HR in vasodilatory septic shock patients exposed to a fixed dose of 0.067 U/min (Dunser 2003). Similar results were reported by others with 0.033 U/min and 0.067 U/min dose. No dose-dependency was reported (Torgersen 2010). No effect on HR was reported with doses of 0.04 U/min infused for 24 h (Malay 1999) or doses of 0.01-0.08 U/min for 4 h (Patel 2002).

A retrospective analysis conducted by Argenziano 1999 in patients who developed hypotension after cardiac transplantation reported a decrease in HR 1-2 h after administration of 0.1 U/min AVP. Decrease in HR was reported with doses between 0.06 and 0.1 U/min over 2 days (Dunser 2002).

##### Cardiac Index/output (CI/CO):

In vasodilatory septic shock either no change or decrease in CO/CI was observed with AVP. No change in CI was reported with 0.04 U/min AVP (Malay 1999), a transient decrease in CI was observed with doses ranging 0.04-0.20 U/min (Lauzier 2006). A decrease in CI was reported in a retrospective analysis with doses ranging from 0.01 to 0.6 U/min (Holmes 2001).

The same trend was reported in postcardiotomy vasodilatory shock patients. A retrospective analysis conducted by Argenziano 1999 in patients who developed hypotension after cardiac transplantation reports a decrease in CO/CI 1-2 h after

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

administration of 0.1 U/min AVP. However, no change in CI/CO was observed with the same AVP dose administered for over 2 days by others (Dunser 2002).

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

#### Ischemic skin lesions

In Dunser 2003, the occurrence of clinical complications during the study period is as follows: 7 of 24 AVP patients (29.2%) and 6 of 24 NE patients (25%) developed new ischemic skin lesions (P=1).

#### Digital ischemia

Russell 2008 reported that the incidence of digital ischemia was higher in the AVP (0.01-0.03 U/min) than in the NE arm. These doses of AVP used in septic shock patients are considered low.

Digital ischemia is also reported with low doses of AVP in children with septic shock (Choong 2009).

#### GI ischemic lesions

One septic shock patient of the NE group died of total intestinal ischemia and necrosis during the study period and none in the AVP group (Dunser 2003).

Acute mesenteric ischemia was a serious adverse events reported in septic shock patients treated with low doses (0.01 to 0.03 U/min) of AVP by Russell 2008.

Escalating AVP doses infused at 1.2, 2.4, and 4.8 U/h (corresponding to doses of 0.02, 0.04, and 0.08 U/min) in 8 patients with postcardiotomy shock show reduced jejunal mucosal perfusion and increased arterial-gastric mucosal carbon dioxide partial pressure (pCO<sub>2</sub>) gradients; with no evidence of mesenteric ischemia reported in any of these patients (Nygren 2009).

### **7.4.2 Laboratory Findings**

#### Bilirubin and Platelets

Increase in bilirubin and decrease in platelets were reported in septic shock patients with up to 48 h infusion with a 0.067 U/min AVP dose; no changes were found in the NE arm (Table 12).

**Copyright Material Withheld**

Source: Dunser 2003, Table 3

Other authors using similar AVP doses (0.03 and 0.067 U/min) did not find changes in bilirubin and platelet statistically different from baseline (Torgersen 2010).

Two retrospective studies (n=300, Luckner 2005, 2007) reported decreased platelet counts and elevated bilirubin and liver enzymes after AVP doses of 0.033 and 0.067 U/min, particularly among patients undergoing hemofiltration

Reviewer's comments: Thrombocytopenia is common in severe sepsis<sup>9</sup> and a low platelet count is predictive of a poor outcome. Therefore, the effect on platelets could be linked to the disease rather than AVP. However, Dunser 2003 reports that the decrease in platelet and increase in bilirubin is seen only in patients exposed to AVP (see Table 12).

#### 7.4.3 Vital Signs

Vital signs include BP (increase) and HR (decrease). No additional vital signs were reported.

#### 7.4.4 Electrocardiograms (ECGs)

No thorough QT study was conducted for AVP.

#### QT prolongation and TdP

##### **Kelly 1980** (1.3 U/min)

A 48-year-old woman without known history of cardiovascular disease was treated with AVP for hemorrhage from esophageal varices. Subject had a recurrent alcoholic

---

<sup>9</sup> Yaguchi A, Lobo FLM, Vincent JL, Pradier O. Platelet function in sepsis. *Journal of Thrombosis and Haemostasis*, 2004; 2: 2096–2102

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

hepatitis and cirrhosis and was treated for hematemesis. TdP was reported after a bolus injection (IV) of AVP (1.3 U/min over 15 min). Immediately after the bolus, BP rose (from 120/62 to 150/70 mmHg) with a relative bradycardia (64 bpm). Fifteen minutes post infusion 7 to 10 PVC were noted followed by TdP and fibrillation. Event was reverted with xylocaine cardioversion.

**Eden 1983** (0.5 U/min)

A 37-year-old man was admitted with hematemesis. There was no history of hypertension, congestive heart failure, or ischemic heart disease. IV Infusion started at 0.3 U/min and was gradually increased to 0.5 U/min. Periods of sinus bradycardia developed during infusion. Multiform PVC and ventricular bigeminy were more frequent. AVP infusion was tapered (0.2 U/min) and TdP developed, preceded by marked QT prolongation. Electrolytes were normal. AVP was gradually discontinued.

**Mauro 1988** (0.1, 0.2 and 0.4 U/min)

A 54 year old subject with hematemesis due to portal hypertension was given 4U of AVP via IV over 5 min (0.8 U/min), followed by a 0.5 U/min AVP infusion. Four hours later ECG indicated sinus bradycardia with QTc prolongation. Then BP increased and HR slowed to 38 bpm, followed by a short run of TdP which converted spontaneously. AVP infusion rate was reduced to 0.2 U/min. One hour later the patient experienced a second TdP (subject was still bradycardic, 38 bpm, before the episode). Magnesium was low. AVP was reduced to 0.1 U/min. Twelve h later subject developed another TdP that required cardioversion. AVP was discontinued. No further events took place after discontinuing AVP. QT prolongation and TdP occurred while subject was on AVP. Events can be attributed to AVP since subject was not taking other medications, hypomagnesemia may contribute to the event. .

**Faigel 1995**

Three cases of QT prolongation and TdP in cirrhotic patients treated with 0.4 U/min AVP. All three subjects were treated with QT prolonger medications (droperidol and haloperidol) and 2 out of three had condition that favors the arrhythmia (hypokalemia and hypomagnesemia), AVP may contribute to the TdP synergistically with these factors.

**Kupferschmidt 1996**

This is a report of three patients treated with AVP to stop bleeding esophageal varices due to portal hypertension. Bradycardia was the common finding in the three subjects and one of them developed TdP afterwards. The dose used is not reported.

Cardiac Arrest

Russell 2008 reported 8 cardiac arrests in the NE groups whereas 3 were reported in the AVP group. A previous study raised the possibility that AVP may increase the

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

incidence of cardiac arrest<sup>10</sup>. Because this is a seriously ill population it is difficult to conclude whether these events were due to AVP or the underlying condition.

### Tachyarrhythmias (TA)

In Dunser 2003 TAs were defined as non-sinus rhythm with HR exceeding 100 bpm. Twelve-lead ECG examinations and serum troponin I determinations were performed before study entry and 24 and 48 h after study entry to scan for myocardial ischemia or infarction.

A significant difference in the incidence of new-onset TA between AVP and NE arm was observed in this study conducted in 48 patients with CA-resistant vasodilatory shock. Two of 24 patients (8.3%) receiving AVP developed new-onset tachycardic atrial fibrillation, whereas 14 of 24 NE patients (54.3%) experienced new-onset atrial fibrillation during the observation period ( $P < 0.001$ ).

#### 7.4.6 Immunogenicity

The immunogenicity of AVP is expected to be very low.

## **7.5 Other Safety Explorations**

### 7.5.1 Dose Dependency for Adverse Events

Luckner 2007, performed a retrospective analysis for the 0.033 and 0.067 U/min AVP doses to search a dose-response relationship for hemodynamic and safety measurements. A dose relationship was observed for hemodynamic parameters such as MAP and SVR (not shown) and for total bilirubin increase. No dose response was observed for platelet decrease (Table 13).

---

10 Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001;27:1416-21.

**Copyright Material Withheld**

Source: Luckner 2007, Adapted from Table 3

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

A bacterial mutagenesis (Ames) and CHO chromosome aberration assays were conducted by the Sponsor for safety assessment of AVP and AVP degradation products (b) (4) to evaluate the mutagenic potential of AVP. AVP did not show any genotoxic potential in mutagenicity and clastogenicity studies.

The Sponsor did not conduct any formal carcinogenic study

### **7.6.2 Human Reproduction and Pregnancy Data**

There are no adequate or well-controlled studies of AVP in pregnant women. Animal reproduction studies have not been conducted with AVP. The sponsor did not conduct fertility impairment studies in animals. Some human and animals published data suggest that AVP induces uterine contractions suggesting a potential risk to the developing embryo and fetus.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

The safety information from children with vasodilatory shock treated with AVP is insufficient. As a postmarketing requirement, the sponsor will be asked to submit for review data from the 4 studies conducted in children: the randomized, double blind controlled study (Choong 2009), and the 3 retrospective studies (Lechner 2007, Rosenzweig 1999, Alten 2012). Serious adverse events and deaths reported (Choong 2009) will then be reviewed in greater detail.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reports of abuse potential or withdrawal/rebound.

##### Overdose:

There have been reports of TdP in cirrhotic patients treated off-label (hematemesis) with AVP doses > 5-times the maximal proposed dose.

## 8 Postmarket Experience

From reviewer's data mining postmarketing search and literature search

### Skin effects

**Skin-AERS data mining: case number 304389.** 52-year old man developed skin necrosis after treatment with AVP to control bleeding of the esophagus. Man has history of liver cirrhosis. The man was treated previously with AVP 0.4 U/min for 8 days and in another occasion treated with 0.13-0.2 U/min for 11 days and no lesions were observed. The third time the AVP dose used was 0.8 U/min + continuous infusion of DA. Signs and symptoms of necrosis developed 58 h after starting AVP.

**Skin-AERS data mining: case number 6244044:** An 84 year old male patient received an iv infusion of AVP 0.02 U/min for hypotension due to severe septic shock refractory to NE, at an unknown day patient developed skin necrosis<sup>11</sup>.

### Published literature (Pubmed)

In a retrospective analysis, Dünser<sup>12</sup> reported a 30.2% incidence of ischemic skin lesions (including distal limbs, trunk, and tongue) in 63 critically ill patients with CA-resistant vasodilatory shock who received continuous AVP infusion at rates of 0.06–0.1 U/min. Ischemic skin lesions (ISL) developed in 19 of 63 patients (30.2%). Thirteen of 19 patients (68%) developed ISL of distal limbs, 2 patients (10.5%) developed ISL of the trunk, and 4 patients (21%) developed ISL in distal limbs and in the trunk. Five patients (26%) had additional ischemia of the tongue. Preexistent peripheral arterial occlusive disease and presence of septic shock were independently associated with the development of ISL during AVP therapy (Table 14).

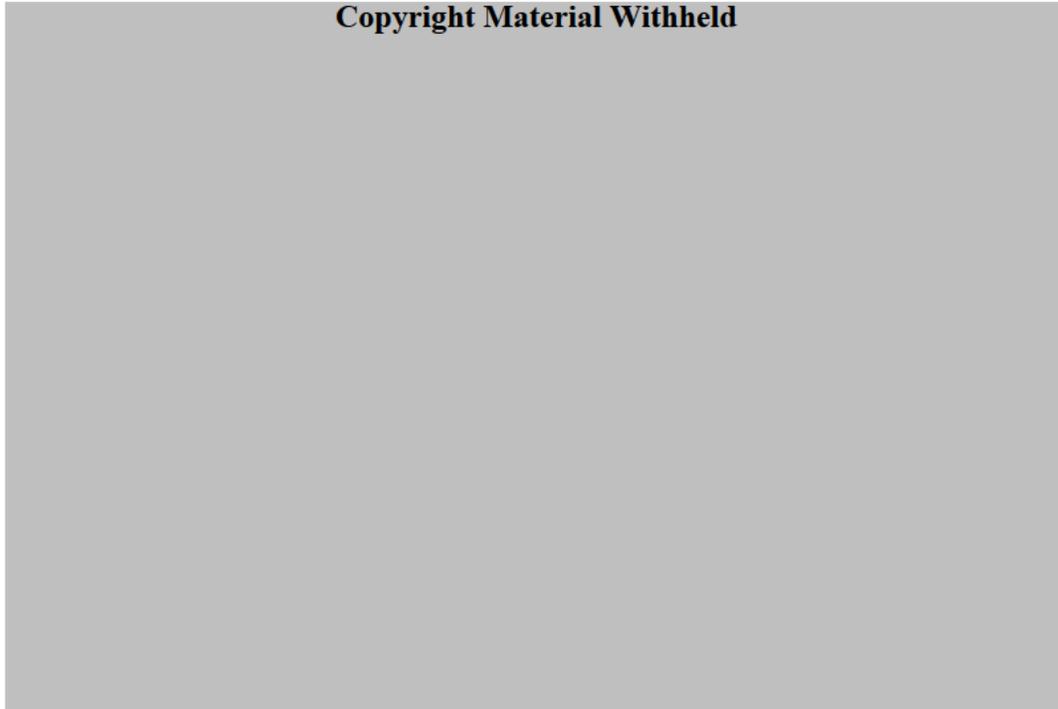
---

11 Kim EH et al., 2006, Korean J Intern Med 21:287-90

12 Dünser MW, Mayr AJ, Tür A, Pajk W, Barbara F, Knotzer H, Ulmer H, Hasibeder WR. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med. 2003 31:1394-8.

**Table 14- Baseline characteristics of Patients with Ischemic Skin Lesions (Dunser 2003)**

**Copyright Material Withheld**



## **GI effects**

### Published literature

Two studies reported AVP effect on gastric mucosal perfusion in patients with septic shock and one in post cardiectomy vasodilatory shock.

One of the studies used a 0.04 U/min 4 h infusion in 12 patients (between 40 and 89 years of age) with severe septic shock<sup>13</sup>. The remarkable result was that gastric mucosal PCO<sub>2</sub>-gap increased significantly from 13.3 [8.0 –16.7] to 17.1 [10.3–28.7] mmHg, with AVP infusion. Same authors<sup>14</sup> found in septic shock patients that higher doses of AVP (0.06 –1.8 U/min) further increased gastric PCO<sub>2</sub> gap (from 17.5±26.6 to 36.5± 26.6 mm Hg, (p < .01), suggesting that gut blood flow could have been redistributed away from the mucosa.

---

13 Klinzing, S, Simon, M, Reinhart, K, Meier-Hellmann, A, Sakr, Y, Moderate-dose Vasopressin Therapy May Impair Gastric Mucosal Perfusion in Severe Sepsis. *Anesthesiology*, 2011, 114: 1396-1402

14 Klinzing, S, Simon, M, Reinhart, K, Bredle, D, Meier-Hellmann A., High-dose vasopressin is not superior to norepinephrine in septic shock. *Crit Care Med* 2003 31: 2646-50

Clinical Review  
 Mónica L. Fiszman, M.D., Ph.D.  
 NDA # 204-485  
 Vasopressin

Similar results were reported in 8 post cardiectomy patients with vasodilatory shock. Incremental doses of AVP (1.2, 2.4 and 4.8 U/h; 0.02, 0.04 and 0.08 U/min respectively), were infused for 30 min at each infusion rate. The infusion rate of NE was simultaneously modified to maintain MAP at a target level of 75 mmHg. Increasing doses of AVP decreased jejunal mucosal perfusion, and increased the arterial-gastric-mucosal pCO<sub>2</sub> gradient.<sup>15</sup>

**FAERS search**

As per the medical reviewer request the Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Event Reporting System (FAERS) for postmarket adverse event cases with a serious outcome for adult and pediatric patients with Pitressin (vasopressin) injection.

The FDA Adverse Event Reporting System (FAERS) and Empirica data mining were searched with the strategy described in Table 15 and Table 16.

**Table 15-FAERS Search Strategy**

<b>FAERS Search Strategy</b>	
Date of search	January 2, 2013
Time period of search	January 1, 1968 to January 2, 2013
Product Terms	Vasopressin, Vasopressin Tannate, Pitressin
MedDRA Search Terms	All adverse events
Additional criteria	<i>Serious</i> outcome
Age criteria	Search 1: 18 years of age or older (adult patients) Search 2: 17 years of age or younger (pediatric patients)

**Table 16- Empirica Signal Search Strategy**

<b>Data Mining Search Strategy</b>	
Data Refresh Date	August 27, 2012
Product Terms	Vasopressin
Empirica Signal Run Name	Generic by Age, Suspect Drugs only
MedDRA Search Strategy	All Adverse Events

<sup>15</sup> Nygren A, Thore´n A, Ricksten SE: Vasopressin decreases intestinal mucosal perfusion: A clinical study on cardiac surgery patients in vasodilatory shock. Acta Anaesthesiol Scand 2009; 53:581– 8

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

As of January 2, 2013, FAERS retrieved 88 cases in adults ( $\geq 18$  years) and 16 cases in children (0-17 years ) with serious outcome with AVP use.

**Table 17- Total number of FAERS reports with a serious outcome**

<b>Total number of FAERS reports for vasopressin with a serious outcome*</b>		
All events from January 1, 1968 to January 2, 2013		
	<b>Serious<sup>‡</sup> (US)</b>	<b>Death (US)</b>
<b>Adults (<math>\geq 18</math> years)</b>	88 (46)	33 (10)
<b>Pediatrics (0-17 years)</b>	16 (5)	7 (2)
<b>Total</b>	104 (51)	40 (12)

\* May include duplicates and have not been assessed for causality

^ US counts in parentheses

‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

The most common PT in the pediatric population was rhabdomyolysis. In adults most common PT were hypotension, rhabdomyolysis and cardiac arrest.

See Table 18 and Table 19 FAERS Crude Counts of All Preferred Terms in Cases.

**Table 18-Pediatric Cases with Serious Outcome**

<b>Most Frequently Reported MedDRA PTs with N<math>\geq 2</math> for Vasopressin in pediatric cases with serious outcome received by FDA as of January 2, 2013.</b>		
<b>Preferred Term</b>	<b>Count of Events</b>	<b>Percent of Total Cases</b>
Rhabdomyolysis	4	25%
Acidosis	2	12.50%
Bacteraemia	2	12.50%
Hyperkalaemia	2	12.50%
Platelet count decreased	2	12.50%
Renal failure acute	2	12.50%
Bradycardia	2	12.50%
Necrotizing fasciitis	2	12.50%
Pulmonary embolism	2	12.50%
Pulmonary hypertension	2	12.50%
Right ventricular hypertrophy	2	12.50%
Tricuspid valve incompetence	2	12.50%

% of Total: The total number of cases may not sum because a case may contain more than one event term. The percent count of cases for each term is based on the count of PTs divided by the total count of cases

**Table 19- Adult Cases with Serious Outcome**

<b>Most Frequently Reported MedDRA PTs with N≥4 for Vasopressin in adult cases with serious outcome received by FDA as of January 2, 2013.</b>		
<b>Preferred Term</b>	<b>Count of Events</b>	<b>Percent of Total Cases</b>
Hypotension	14	15.91%
Rhabdomyolysis	12	13.64%
Cardiac arrest	9	10.23%
Bradycardia	7	7.95%
Myopathy	7	7.95%
Renal failure acute	7	7.95%
Blood creatine phosphokinase increased	6	6.82%
Diabetes insipidus	6	6.82%
Pulmonary oedema	6	6.82%
Drug ineffective	6	6.82%
Death	5	5.68%
Hypernatraemia	5	5.68%
Hyponatraemia	5	5.68%
Pulse absent	5	5.68%
Blood pressure decreased	4	4.55%
Drug interaction	4	4.55%
General physical health deterioration	4	4.55%
Optic ischemic neuropathy	4	4.55%
Pneumonia	4	4.55%
Respiratory failure	4	4.55%
Toxicity to various agents	4	4.55%

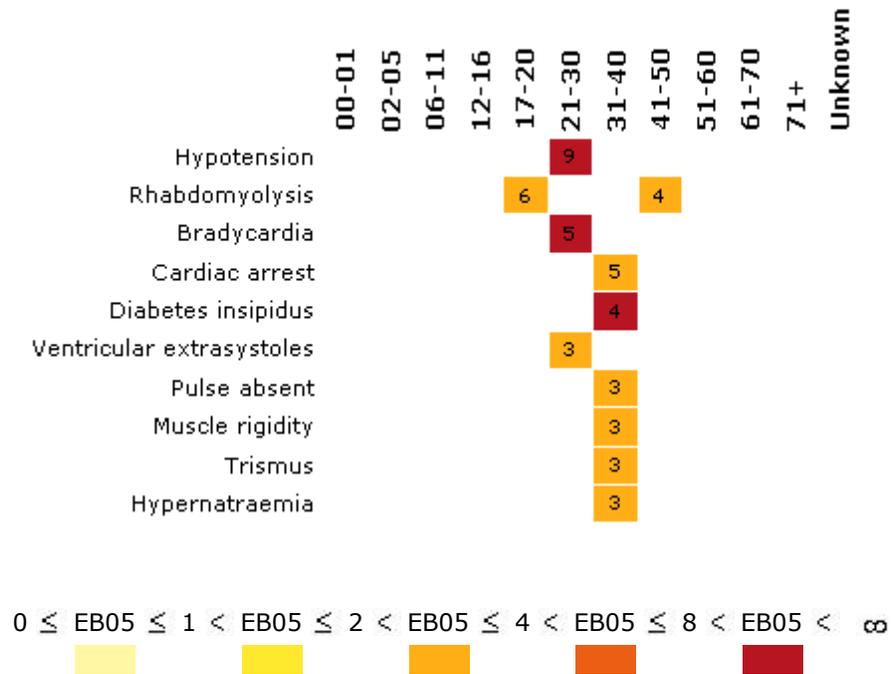
Reviewer's comments: Rhabdomyolysis is a relatively common adverse event reported immediately after a significant burn. Some of the reports of these events, with AVP being a co-medication, are published <sup>16</sup>. In all the cases AVP was listed as a co-suspect, it is not possible to conclude about AVP being the culprit in these events.

### **Data Mining of FAERS using Empirica Signal**

Data mining safety signals with AVP in various age groups are illustrated in the graph below. The rows list the Preferred Terms (PTs) or single medical concepts and the columns list the age ranges. The numbers in the tiles indicate the number of adverse event reports and the colors indicate the various EB05 scores. The darker the tiles, the higher the EB05 score. An additional restriction for this graph is EB05 scores of at least greater than 2. Typically, EB05 scores greater than 2 indicate a potential safety signal. No cases (no safety signals) were identified in patients ≤ 16 years of age.

<sup>16</sup> Bache SE, Taggart I, Gilhooly C Late-onset rhabdomyolysis in burn patients in the intensive care unit. Burns 37 (2011) 1241-1247.

Figure 3- 2012 Data Mining results- PTs with EB05 scores >2



## 9 Appendices

### 9.1 Literature Review/References

#### 9.1.1. Vasodilatory Septic Shock (Adults)

##### Prospective randomized double-blind controlled studies

Malay (1999)

**Title:** Low-Dose Vasopressin in the Treatment of Vasodilatory Septic Shock

**Primary endpoint:** hemodynamic response as defined by an increase in arterial BP. Authors did not specify SBP, MAP or DBP.

**Secondary endpoint:** time to CA pressor-free hemodynamic stability. This is defined as a MAP more than 70 mmHg for more than 30 min in the absence of any known vasopressor agent except the study drug and /or low-dose DA infusion (3 µg/kg/min).

**Subjects:** patients > 18 years of age with vasodilatory septic shock admitted to the trauma intensive care unit.

**Study Design:** Double-blind placebo-controlled study. Patients were randomized to receive either AVP 0.04 U/min (n=5) or placebo (n=5). Placebo was normal saline+vasopressors. Open-label vasopressors were NE, PHE and DA. These drugs were weaned and discontinued provided that the MAP remained more than 70 mm Hg. All patients had an indwelling arterial line to assess MAP. CO was determined by the thermodilution technique and performed in triplicate. Hemodynamic parameters were recorded at baseline and 1, 4, 8 and 24 h.

**Safety monitoring:** Bradycardia, arrhythmias, myocardial and/or mesenteric ischemia or infarction and deaths.

##### **Results:**

**Subjects:** Ten patients were enrolled and randomized. NE requirements varied widely between subjects within each group: mean 12 (0-25) for the placebo group and 6.8 (4-30) for the treated group. Baseline MAP was 66 mmHg in the placebo group and 64 mmHg in the AVP group.

**Hemodynamic:** AVP administration increased MAP, SBP and SVR (see Table 5). All these parameters were unchanged in the placebo group. Interestingly, AVP did not decrease HR and CI, two commonly reported effects with AVP.

**Safety:** Two patients under placebo died (1 at 8 h and the other at 18 h post-treatment) because of refractory hypotension despite receiving standard CA. Therefore the secondary endpoint measured at 24 h was determined in 3 out of 5 subjects in the

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

placebo group. Due to this decrease in sample size a valid statistical analysis for the secondary endpoint was not performed. AVP decreased the need of open label vasopressor. There were no post-baseline changes in sodium, base deficit or creatinine in the study.

**Comments:** This was a randomized double-blind study, and therefore risk of bias was minimized, but had the limitation of a small sample size. Two study subjects under placebo died. The reason of death was refractory hypotension suggesting that AVP has an effect over background medication.

Russell (2008).

**Title:** Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock.

**Date of study and location:** This trial was conducted between July 2001 and April 2006 in 27 centers in Canada, Australia, and the United States.

**Endpoints:**

- Primary: mortality rate 28 days after the start of infusions.
- Secondary: 90-day mortality; days alive and free of organ dysfunction during the first 28 days according to the Brussels criteria; days alive and free of vasopressor use, mechanical ventilation, or renal replacement therapy; days alive and free of the systemic inflammatory response syndrome (SIRS); days alive and free of corticosteroid use; and length of stay in the ICU.

**Study population:** Subjects older than 16 years of age who had septic shock resistant to fluids and low-dose NE (< 5 µg/min).

Exclusion criteria: unstable coronary syndrome, time elapsed since the patient met entry criteria > 24 h, previous use of open-label AVP for BP support during the current hospital admission, malignancy or other irreversible disease with an estimated six-month mortality ≥ 50 %; subject has a proven or suspected acute mesenteric ischemia; death anticipated within 12 hrs, underlying chronic heart disease (NYHA class III or IV) and shock, severe hyponatremia (serum sodium < 130 mmol/L), traumatic brain injury, Raynaud's phenomenon, systemic sclerosis or vasospastic diathesis, pregnancy, cases in which physician was not committed to aggressive care.

**Study design:** This is a randomized, double-blind trial. The estimated sample size was 776 in order to detect an absolute 10% difference in mortality, assuming a mortality rate of 60% in the NE group and a two-sided alpha error of 0.05 and a power of 80%.

Patients who had septic shock and were receiving a minimum of 5 µg of NE /min were randomized to receive either AVP (0.01 to 0.03 U /min) or NE (5 to 15 µg/min) in addition to open-label vasopressors. The study population was stratified by center and by severity of shock in the hour before randomization. The stratum of less severe septic shock was defined as treatment with 5 to 14 µg of NE/min, and the stratum of more severe shock was defined as treatment with ≥ 15 µg/ min of NE or equivalent.

**Dosing:** The blinded AVP infusion was started at 0.01 U /min and titrated (every 10 min) to a maximum of 0.03 U /min, whereas the blinded NE infusion was started at 5 µg/ min and titrated to a maximum of 15 µg/min. Open-label vasopressors were titrated to

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

maintain a constant target MAP (65 to 75 mmHg) if not reached with study drug infusion.

**Study drug discontinuation:** if a serious AE occurred (ST-segment elevation, serious or life-threatening (hemodynamically unstable) cardiac arrhythmias, acute mesenteric ischemia, digital ischemia, or hyponatremia (serum sodium level, <130 mmol/L), or patient's condition improved.

## Results

### Baseline

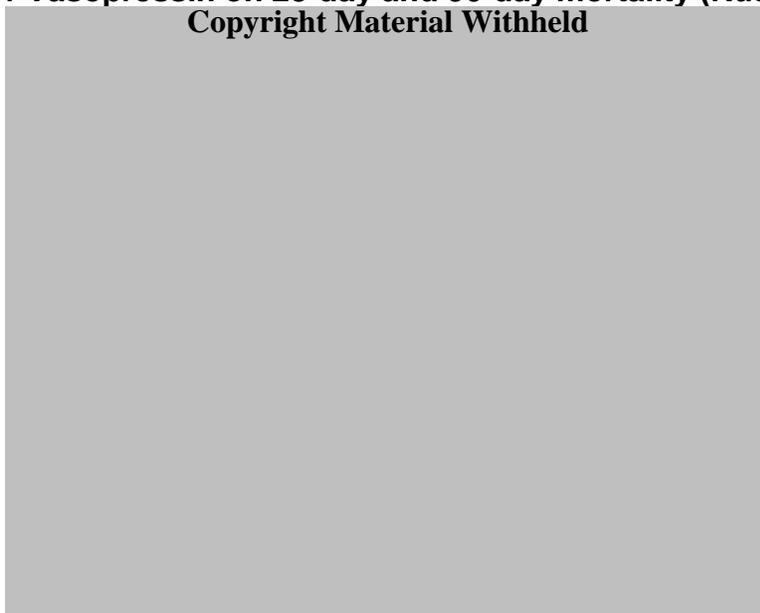
From the 6229 screened 779 patients underwent randomization and infusion of study drug, 778 were included in the primary analysis: 396 in the AVP group and 382 in the NE group. Mean age of enrolled patients in both groups was about 60 years. Patients were severely ill in both groups as indicated by the APACHE II<sup>17</sup> score ( $27 \pm 6.9$ , NE group;  $27 \pm 7.7$ , AVP group), by the high NE requirements ( $20.7 \pm 18$   $\mu\text{g}/\text{min}$ , NE group;  $20.7 \pm 22$ , AVP group) and lactate levels (3.5 mmol/L, both groups). In both groups 100% of the subjects had cardiovascular failure, the majority of the patients (85%) had respiratory failure, and a significant proportion had renal failure (67%). It is interesting to note that MAP at baseline was relatively high (73-72 mmHg, NE and AVP group respectively) compared to other publications with same patient population. No SVR data were reported.

No statistically significant difference was observed between the AVP and NE groups in the primary outcome (rate of death from any cause, assessed 28 days after the start of infusions; 35.4%, AVP and 39.3%, NE respectively;  $P = 0.26$ ). No difference in mortality at 90 days (43.9% and 49.6%, respectively;  $P = 0.11$ ) was observed. A trend in favor of AVP compared to NE was observed. In this study the AVP effect on 28-day and 90-day mortality was similar to that observed with NE. (Figure 4)

---

17 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.

**Figure 4-Vasopressin on 28-day and 90-day mortality (Russell 2008)**  
Copyright Material Withheld



There was no significant difference among both groups in any of the secondary endpoints.

Safety. The overall rate of SAE was 10% in each group. More patients in the AVP group had digital ischemia which is an expected AE observed with AVP and other vasoconstrictors. Cardiac arrest with AVP has been reported previously. Mesenteric ischemia was reported as well as digital ischemia both are expected AE with AVP (see Table 7).

**Comments:** This study compares the effect of AVP to NE. Was a randomized double-blind study and therefore the chances of bias were very low. The study failed to demonstrate a difference in the primary endpoint: 28-days mortality (mortality rate in NE vs AVP). However, a trend toward higher survival rate in the AVP group is reported. The fact that AVP survival rate is similar to NE, is reassuring. Moreover, AVP increase MAP at the same extent as NE.

MAP at baseline was relatively high (73-72 mmHg, NE and AVP group respectively) as compared with other publications with similar patient population. These BP values do not imply that the population was healthier. As in many of the studies conducted with this type of patients, there is some background therapy that affects the interpretation of results, in this case the bedside nurse titrated open-label vasopressors to maintain a constant target MAP. An initial target MAP of 65 to 75 mm Hg was recommended; however, the attending ICU physician could modify the target BP of each patient. Open-

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

label vasopressors were increased only if the target MAP was not reached on maximal study drug-infusion.

The high NE requirements may suggest that MAP was kept by open label CA at the time of randomization and subjects were CA resistant based on the high NE requirements reported at baseline.

**Safety:** A previous study raised the possibility that AVP may increase the incidence of cardiac arrest<sup>18</sup>. In this study 8 cardiac arrests were reported in the NE groups whereas 3 were reported in the AVP group. Because of the limited information available it is hard to conclude whether these events were due to AVP or the underlying condition. Reported digital ischemia and mesenteric ischemia are expected AE with AV.

Patel (2002)

**Title:** Beneficial Effects of Short-term Vasopressin Infusion during Severe Septic Shock

**Date of study and location:** not published

**Endpoints:** The objective of the study was to examine the vasopressor sparing effect while maintaining hemodynamic stability and adequate end-organ perfusion (urine output and creatinine clearance, gastric mucosal carbon dioxide tension, and electrocardiogram ST segment position were evaluated).

**Subjects:** 24 patients experiencing severe septic shock who required high-dose vasopressors despite adequate fluid resuscitation were randomized to NE (n=11) or AVP (n=13), and open-label vasopressor. High-dose vasopressor support was defined as follows: NE dose ( $\mu\text{g}/\text{min}$ ) plus EPI dose ( $\mu\text{g}/\text{min}$ ) plus DA dose divided by 4 ( $\mu\text{g}/\text{kg}/\text{min}$ ) greater than 5 for a minimum of 1 h. The subjects excluded had present or suspected acute coronary artery disease, had acute mesenteric ischemia present or suspected, severe hyponatremia (serum sodium < 125 mM) not responding to water restriction, Raynaud phenomenon, systemic sclerosis or vasospastic diathesis.

**Study design:** prospective, double-blind, randomized, controlled study. Infusion of AVP or NE was given in a double-blind fashion for 4 h. During the initial 60 min of this 4-h infusion protocol, the study drug was titrated (every 5–10 min), and the prestudy vasopressor agent (NE) was titrated down to keep MAP constant. All other medications were held constant. At the end of the 4-h study drug infusion period, a second set of measurements was obtained to complete the study. The starting dose of AVP was 0.01 U/min and the highest tested was 0.08 U/min; NE starting dose was 2  $\mu\text{g}/\text{min}$  and maximal dose was 16  $\mu\text{g}/\text{min}$ . The volumes injected were between 7ml/h to 56 ml/h.

---

18 Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001;27:1416-21.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Results:** Baseline characteristics were similar between both groups.

The primary endpoint was statistically significant between the two groups. In the AVP group, the NE infusion decreased from 25.0 µg/min (20.0, 37.3 µg/min) pre-study to 5.3 µg/min (0, 8.0 µg/min; P <0.001) at 4 h while maintaining MAP (table 3). The median AVP infusion rate in this group was 0.06 U/min (0.05, 0.06 units/min). Neither NE nor AVP administration induce post baseline changes in any of the hemodynamic variables.

**Table 20- Vasopressin-Hemodynamic Effects (Patel 2002)**  
Copyright Material Withheld

AVP infusion increased urine output and creatinine clearance from baseline to 4 h with no change in fractional excretion of sodium. There was an improvement in renal function after 4 h of AVP infusion and no changes in renal function were observed after 4 h of NE infusion. Neither NE nor AVP affected gastric–arterial PCO<sub>2</sub> gradient or altered ST segment in the ECG.

### **Comments**

This was prospective, double-blind, randomized, and controlled study. Infusion of AVP or NE was given in a double-blind fashion for 4 h. The primary endpoint was achieved in this study i.e., AVP decreases significantly NE requirements. Major drawbacks are the low sample size, and the short duration (4h).

### **Prospective randomized open-label studies**

Dunser (2003)

**Title:** Arginine Vasopressin in Advanced Vasodilatory Shock A Prospective, Randomized, Controlled Study

**Study date and location:** Single center study conducted from February 2001 through April 2002. The study was performed at the Division of General and Surgical Intensive Care Medicine, Leopold Franzens University of Innsbruck, Austria.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Primary endpoint:** to evaluate differences in hemodynamics between groups during the 48-h observation period.

**Secondary endpoint:** changes in other single-organ functions, including tonometrically derived gastric parameters during the study period.

**Study population:** Patients enrolled had CA-resistant vasodilatory shock related to cardiovascular surgery or to SIRS, both with and without sepsis; and MAP < 70 mm Hg despite adequate volume resuscitation, and with NE requirements exceeding 0.5 µg /kg/min.

### Study design

- This is a randomized, controlled study, 48 patients were enrolled. Drugs were administered in an open-label fashion.
- The patients were randomly assigned into an AVP group or NE group
- Observational period was 48 h.
- Efficacy: HR, MAP, mean pulmonary arterial BP, pulmonary capillary wedge pressure, and cardiac and stroke volume indices were recorded in all patients and documented together with NE and milrinone requirements before study entry, and at 1, 12, 24, and 48 h after study entry. SVRI, left ventricular stroke work index (LVSWI), systemic oxygen transport, and consumption index were calculated according to standard formulas.
- Safety: incidence and types of new-onset TAs were monitored during the study. TAs were defined as nonsinus rhythm with HR exceeding 100 bpm. Twelve-lead ECG examinations and serum troponin I determinations were performed before study entry and 24 and 48 h after study entry to scan for myocardial ischemia or infarction. Other safety data collected were new onset myocardial ischemia/infarction, occurrence of ischemic skin lesions, number of patients on veno-venous hemofiltration, and gastrointestinal perfusion (tonometry).

### Statistics

Sample size: pre-calculated on the basis of a previous retrospective study. To detect clinically relevant differences in main outcome variables and assuming an alpha error of 0.05 and a power of 80%, a sample size of at least 20 patients in each group was needed. The number of patients enrolled was increased to 48 to compensate for death-related data dropout.

Differences in hemodynamic and single-organ variables between groups and within repeated measurements were analyzed by using linear mixed-effects models to account for death-related dropouts. Main effects between groups and within repeated measurements were given and considered to indicate statistical significance if <0.05.

Safety endpoints: incidence of new-onset TAs and myocardial ischemia/infarction, occurrence of ischemic skin lesions, and number of patients on veno-venous hemofiltration were compared with the use of Student's t tests,  $\chi^2$  tests, or Mann-Whitney *U* tests, as appropriate.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Dose/administration:** infusion of AVP at a constant rate of 4 U/h (0.067 U/min). NE infusion was adjusted to maintain MAP  $\geq$ 70 mm Hg. When NE requirements decreased to  $<$  0.3  $\mu$ g/kg/min AVP infusion was tapered off stepwise according to the response of MAP to AVP reductions. In NE patients, MAP  $>$ 70 mm Hg was achieved by adjusting NE infusion as necessary. For those patients in whom NE requirements exceeded 2.26  $\mu$ g/kg/ min, the study protocol was abandoned, and additional AVP infusion was initiated at 4 U/h.

Treatment arms: AVP (0.067 U/min) +NE vs NE

## Results

### Baseline

Study subjects were balanced between the two groups. Subjects included 29% with SIRS (for AVP and NE arm) 29 and 33% with septic shock (AVP and NE arm respectively) and 41 (AVP) and 37.5 % (NE) for postcardiotomy shock

### Hemodynamic:

AVP decreased HR (P=0.033), increased MAP (P<0.001) significantly at all postbaseline time-point tested and decreased NE needs significantly at 24 and 48 h after starting infusion (P=0.001). In both groups, 75% of patients (18 of 24) received a continuous milrinone infusion.

### AEs and Laboratory

NE patients developed significantly more new-onset TAs than AVP patients (54.3% versus 8.3%). Two of 24 patients (8.3%) receiving AVP developed new-onset tachycardic atrial fibrillation, whereas 14 of 24 NE patients (54.3%) experienced new-onset tachycardic atrial fibrillation during the observation period (P<0.001). There were no differences in the incidence of myocardial ischemia and myocardial infarction between groups. Two NE patients developed myocardial ischemia, and 1 NE patient developed myocardial infarction during the study. There were no differences in troponin I values between AVP and NE patients..

Skin and GI: 7 of 24 AVP patients (29.2%) and 6 of 24 NE patients (25%) developed new ischemic skin lesions (P=1). One patient of the NE group died of massive intestinal ischemia and necrosis during the study period.

Postbaseline arterial lactate and platelets decreased significantly. Bilirubin increased significantly. No change in creatinine was reported.

## Comments

Forty-eight patients with catecholamine-resistant vasodilatory shock (with and without sepsis) were prospectively randomized to receive a combined infusion of AVP (0.067 U/min) and NE or NE infusion alone. Drugs were administered open-label therefore bias is expected.

AVP increased MAP. From the total, 8% of the patients in the AVP arm developed new-onset TAs (AFib) whereas 14 of 24 NE patients (54.3%) experienced new-onset atrial fibrillation.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Laboratory measurements indicate a decrease in platelet and an increase in bilirubin in the AVP arm, no change in these laboratory measurements were seen in the NE arm.

Lauzier (2006)

**Title:** Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial

**Study date and number of sites:** Between August 2000 and June 2004 the study was conducted in two sites.

**Study population:** Patients were eligible if they (a) met criteria for septic shock, (b) had at some point MAP pressure of 60 mmHg or less after at least a 1000-ml crystalloid bolus, (c) were on vasopressors for less than 12 h before randomization, (d) had pulmonary artery occlusion pressure of 12 mmHg or higher, and (e) had a CI of 3 l/min/m<sup>2</sup> or higher.

**Study design:** Randomized, controlled, open-label trial.

- Sample size: Twenty-three patients with early (<12 h) hyperdynamic septic shock.
- Duration: Parameters were measured at 0, 1, 6, 12, 24, and 48 h after protocol initiation.
- Hemodynamic measurements: MAP, HR, MPAP, CI, SVRI,
- Safety measurements: Adverse reactions such as ACS, arrhythmias, clinically significant gut and skin ischemia were prospectively and systematically recorded in each group by a physician not involved in the study. ACS was a priori defined as an increase in troponin I level above the normal threshold combined with electrocardiographic (ECG) changes (ST segment elevation or depression of  $\geq 1$ mV or a T wave inversion of  $\geq 2$ mV).
- Data are expressed as mean  $\pm$  SD or median with interquartile range. Differences between groups were analyzed by linear mixed-effects models to consider death-related dropouts. All comparisons with a p value less than 0.05 were considered as statistically significant.
- Dose/administration: AVP (0.04–0.20 U/min) or NE bitartrate (0.1–2.8  $\mu$ g/kg/min), were infused in a central venous catheter to maintain a MAP above 70 mmHg. Other vasopressors were tapered and weaned as the experimental drug was increased. When maximal dosage of the experimental drug was reached (AVP 0.20 U/min; NE 2.8  $\mu$ g/kg/min), administration of the other drug (either NE or AVP) was allowed as rescue therapy if the MAP was still below 70 mmHg. Dobutamine was used if CI decreased below 3 l/min/m<sup>2</sup> despite adequate volume resuscitation
- Comparators: AVP+ OL vasopressors NE+ OL vasopressors

## Results

**Baseline:** Twenty-three patients participated in the study, 13 received AVP. No statistically significant differences were observed between the study groups at

randomization. The mean age was 51 and 58 years in the AVP and NE respectively. Hemodynamic parameters and vasoactive drug requirements were similar at the beginning of drug infusion (NE dose was 0.16 and 0.20 µg/kg/min in the AVP and NE respectively). MAP baseline was 72±7 and 68±10 mmHg and SVR 985±227 and 1108±392 dyne.s.cm<sup>-5</sup> m<sup>-2</sup> in AVP and NE respectively.

**Hemodynamics:** In both groups the MAP increased over time and differed significantly at the end of the study compared with baseline (AVP p = 0.004, NE p = 0.02). However those changes were only seen at 24 and 48 h post-dose for both agents.

No differences were observed between groups (p = 0.74). There was a transient decrease in CI vs. baseline among patients receiving AVP, which was significant at 1, 6, and 12 h (p = 0.02) and was associated with a sustained increase in SVR (p = 0.002). The NE dose was lower in the AVP group at the end of the study compared to baseline, but 85% of AVP-infused patients received NE at some point because their MAP was less than 70 mmHg despite maximal dose of AVP (0.2 U/min).

**Safety:** Three patients died during the study protocol: two in the AVP group and one in the NE group. In each case death was attributed to refractory shock.

One case of acute coronary syndrome occurred during the protocol in each group. In one case the patient had stable coronary artery disease. Coronary angiography demonstrated severe right coronary and circumflex stenosis. The AVP patient had no cardiovascular disease prior to admission, and angiography performed during infusion of AVP at 0.2 U/min revealed an occlusion of a small marginal artery. ECG changes (ST segment depression in lateral precordial leads) subsequently disappeared after tapering the AVP infusion to 0.04 U/min.

### Comments

AVP-induced increase in MAP was observed at 24 and 48 h postdose only. No change in MAP was observed in the first hours of treatment.

Since this study is open label bias cannot be excluded. Another limitations is the difficulty to distinguish between the effect of AVP and OL vasopressors; despite AVP decreased NE requirements, AVP-infused patients received NE at some point because their MAP was less than 70 mmHg despite maximal dose of AVP (0.2 U/min).

Torgersen (2010)

**Title:** Comparing two different arginine vasopressin doses in advanced vasodilatory shock: a randomized, controlled, open-label trial.

**Study date and site:** This single-center study was conducted from 1 January 2008 until 31 December 2008, in a tertiary teaching hospital in Innsbruck, Switzerland.

### Objectives

Primary: to compare the hemodynamic response to AVP at two doses (0.033 vs. 0.067 U/min).

Secondary: differences in organ function and laboratory variables, AVP and prolactin plasma levels as well as the rate of adverse events.

### **Study population-**

Patients with vasodilatory shock due to sepsis, SIRS or after cardiac surgery requiring NE > 0.6 µg/kg/min to maintain a MAP > 60 mmHg were recruited.

Patients were excluded from the study if were < 18 years of age, in a moribund state unlikely to survive > 12h, in whom intensive care was withdrawn, participated in another clinical trial, were pregnant or refused written consent.

Vasodilatory shock was defined as the simultaneous presence of adequate systemic blood flow (CI >2–2.5 l/min/m<sup>2</sup>, mixed venous oxygen saturation > 60%, or an EF >50% together with a HR >80 bpm in the absence of severe diastolic dysfunction on echocardiography), a MAP <60 mmHg in volume-resuscitated patients together with a SVR index <1,200 dyne\*s/cm<sup>5</sup>\*m<sup>2</sup> resulting in the need for NE >0.1 µg/kg/min for >12 h.

### **Study design**

- In this prospective, controlled, open-label trial, patients were randomized to receive a supplementary AVP infusion either at 0.033 U/min (n = 25) or 0.067 IU/min (n = 25).
- Patients were routinely monitored (baseline, 1, 12, 24, 48 h) with an arterial and central venous line. Volume resuscitation was performed according to the response of filling pressures. If the CI remained <2–2.5 l/min/m<sup>2</sup> or mixed venous oxygen saturation <60% despite adequate volume resuscitation and/or blood transfusion, milrinone and/or EPI was continuously infused. After ensuring adequate systemic blood flow using fluids and/or inotropes, NE was infused to increase MAP >60–65 mmHg.
- Sample size: a sample size of 22 patients per group was required to detect a significant difference in the hemodynamic response (MAP increase, decrease in NE requirements) between AVP at 0.033 and 0.067 IU/min (alpha error, 0.05; beta error, 0.2; power, 80%)
- Efficacy measurements: stroke volume index, CI, SVRI, mixed venous oxygen saturation, milrinone requirements
- Safety measurements: decrease in CI or platelet count, increase in liver enzymes or bilirubin
- Dose/administration: One group received 0.067 U/min AVP, and the other 0.033 U/min AVP. After initiation of AVP, NE infusion was adapted to maintain MAP 60–65 mmHg in both groups.

### **Results**

There were no differences in demographic and clinical variables between groups before randomization. AVP infusion increased MAP (0.033 U/min, P= 0.02; 0.067 U/min, P< 0.001) and decreased heart rate (p=0.001 and P<001) in advanced vasodilatory shock irrespective of the dose infused. The reduction in NE requirements was seen in both groups and was marked in the high dose group, being this effect significantly different overtime between groups.

Arterial lactate and base deficit decreased while arterial pH increased in both groups. Decreased platelet was observed with the two doses, but was only significant in the low dose group.

### **Comments**

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

The results demonstrate that AVP increased MAP and SVR and decreased HR. The magnitude of the effect described was similar with the two doses. This is an open label study and bias cannot be excluded. Open label NE was also administered and titrated during the observational period, making the interpretation of data difficult.

### Retrospective studies

Holmes (2001)

**Title:** The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series

This is a retrospective analysis of a database from a single center for cases reported August 1997 through March 1999.

**Objective:** to review all cases of septic shock treated with AVP and to determine the effects on hemodynamic and renal function as well as adverse effects

**Study subjects:** All ICU patients who received AVP for severe septic shock. Subjects included were those who met two out of four criteria for SIRS (temp:  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ ; HR  $> 90$  bpm; respiratory rate  $> 20$  breaths per minute or Pa CO<sub>2</sub>  $< 32$  torr; White cell counts  $12,000$  cells/mm<sup>3</sup>,  $< 4,000$  cells/mm<sup>3</sup> or  $> 10\%$  immature (band) forms) with a documented source of infection who received AVP for a minimum of 2 h. Subject excluded: those that received AVP for GI bleeding or for vasodilatory shock for open-heart surgery.

**Study design:** retrospective analysis

Sample size: 50 patients

Efficacy measurements: MAP, PAP, CI, urine output hourly. Values at baseline (before infusion) and at 4 h, 24 h and 48 h of infusion of AVP were compared.

Safety measurements: the information of the following serious AE was searched: ventricular arrhythmias, acute myocardial infarction or cardiac arrest.

Dose: range 0.01-0.06 U/min

### Results

From August 1997 to March 1999, 91 patients received AVP in the ICU. Fifty patients received AVP for more than 2 h for septic shock. Five of the 50 patients received infusions for less than 4 h and therefore, hemodynamic variables were not recorded. Patients were severely ill, as evidenced by very high APACHE II ( $27 \pm 7$ ) and there was a high prevalence of underlying comorbid disease. The average dose of AVP used in the 48 h of infusion was 0.05 U/min (range 0.01- 0.6 U/min). Hospital mortality was 85%. AVP increased MAP significantly by 18% at 4 h ( $p < 0.001$ ) and remained at that level 24 and 48 h later ( $p = 0.006$  and  $0.008$ , respectively). Systolic PAP remained unchanged on infusion at  $45 \pm 13$  mmHg. Mean CI decreased by 11% at 4 h ( $p = 0.03$ ) and did not change further with time.

Urine output compared to baseline (excluding anuric patients) increased 79% at 4 h ( $p = 0.002$ ) and further increases were not significant for patients still alive and on AVP.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Mean pressor dosage decreased by 33% at 4 h ( $p = 0.001$ ), decreased by 53% at 24 h ( $p = 0.002$ ) and decreased by 48% at 48 h ( $p = 0.01$ ).

Safety: eight patients survived to hospital discharge. The causes of death in the remaining 42 patients were refractory shock ( $n = 20$ ), withdrawal of care due to multiple system organ failure ( $n = 19$  patients), respiratory failure later on the ward ( $n = 2$ ) and cerebral edema due to underlying disease ( $n = 1$ ).

There were six cardiac arrests on AVP infusion, four at relatively high dosages ( $\geq 0.05$  U/min). All patients were in severe refractory shock. One patient had a marked decrease in CI on AVP infusion (0.03 U/min) and died of pulseless electrical activity. The other patients had asystole ( $n = 4$ ) and ventricular fibrillation ( $n = 1$ ).

### **Comments:**

In this retrospective case series, the patients received AVP for severe septic shock. AVP markedly and significantly increased MAP, did not change PAP, markedly increased urine output and decreased vasopressor dosage significantly. Six cardiac arrests were reported while on AVP infusion, all because of deficient vasopressor response.

The study has several limitations. As the authors stated, the patients did not receive AVP according to strict guidelines. Co-interventions such as fluid therapy and steroid use that could also alter the outcome variables are lacking, timing of entry into the study is not standardized (i.e. duration of septic shock varied) so patients could have been at different stages of septic shock at the onset of AVP infusion. This could explain the high mortality rate (85%) i.e, AVP was probably used as "rescue therapy" in patients who appeared to be dying of refractory hypotension.

### 9.1.2. Vasodilatory Postcardiotomy Shock (Adults)

#### **Studies conducted in patients with vasodilatory shock**

##### **Randomized, Placebo-controlled study**

Argenziano (1997)

**Title:** A Prospective Randomized Trial of Arginine Vasopressin in the Treatment of Vasodilatory Shock After Left Ventricular Assist Device (LVAD) Placement

**Study population:** This was a single-center study and participants were patients at the Columbia-Presbyterian Medical Center undergoing LV AD placement for end-stage heart failure.

Subjects were included with MAP  $\leq 70$  mm Hg after weaning from CPB, despite NE administration in excess of 8  $\mu\text{g}/\text{min}$ , and LVAD CI greater than 2.5 L/min/m<sup>2</sup>. Subjects with active peripheral or mesenteric vascular disease or prior administration of arginine AVP were excluded.

**Study design:** This is a prospective randomized blinded study; 10 subjects were evenly randomized to blinded AVP or normal saline. Plasma samples to measure AVP were collected before randomization

- Efficacy measurements: MAP, SVR, LVAD flow and NE dose
- Safety measurements: Not collected.
- Dose/administration: by IV infusion AVP 0.1 U/min.
- A clinical response was defined as an increase MAP >20 mm Hg without an increase in NE administration and/or decrease in NE requirement (>5 µg/min) without a decline in MAP, in the absence of other pharmacological or surgical interventions. In the absence of a clinical response after 15 min of infusion, subjects were eligible at the discretion of the attending surgeon for blinded administration of the alternate solution. If a clinical response was observed, the assigned infusion was continued postoperatively.
- Comparators: AVP compared to saline placebo.

**Results:** Ten (8 men and 2 women) of 23 LVAD recipients met inclusion criteria i.e., decreased MAP ( $60 \pm 2$  mmHg), increase CI ( $2.9 \pm 0.1$  L/min/m<sup>2</sup>), and a requirement for exogenous NE ( $19.7 \pm 5.4$  µg/min) to maintain BP. Despite administration of CA, SVR was low ( $828 \pm 70$  dyne-s/cm<sup>5</sup>), indicating vasodilatory shock.

AVP increased MAP and SVR significantly over baseline values, NE requirements decreased but the change was not significant. AVP rapidly and significantly increased MAP ( $57 \pm 4$  to  $84 \pm 2$  mm Hg,  $p < 0.001$ ) and SVR ( $813 \pm 113$  to  $1188 \pm 87$  dynes-s/cm<sup>5</sup>,  $p < 0.05$ ) in the 5 subjects randomized to receive the hormone.

All parameters remained unchanged in the saline group.

The decrease in NE requirement was not statistically significant. The lack of significance could be explained by the fact that one subject did not have a decrease in NE requirements and by the low sample size ( $n=8$ ).

**Conclusions:** This was a blinded, placebo-controlled, randomized trial, which provided evidence that AVP (at higher doses than those tested for septic shock) is an effective pressor for LVAD recipients with vasodilatory shock. AVP induced a statistically significant increase in MAP and SVR. There was a not statistically significant decrease in NE requirements. The lack of significance could be explained by one unresponsive subject (subject #5), but still there was a clear trend.

Strengths of the study are that study drug was administered blinded, and was compared to placebo. Open label vasopressors dosing was kept constant during the study (15min).

The small sample size and short observation period (15 min duration) are limitations of this study.

### Retrospective studies

Argenziano (1998)

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Title:** Management of Vasodilatory Shock After Cardiac Surgery: Identification of Predisposing Factors and Use of a Novel Pressor Agent.

**Date-study-location:** Data analyzed were from two centers. Departments of Surgery and Medicine, Columbia University College of Physicians and Surgeons, New York. Study date was not specified.

**Objectives:** study consisted of a prospective portion intended to study the incidence of vasodilatory shock in a general cardiac surgery population and predisposing factors. Another section was a retrospective study that analyzed LVAD and OHT clinical databases to find the cases of patients who had received AVP for the treatment of vasodilatory hypotension during a 30-month period. MAP, NE requirements, SVR and CI before and after AVP were reported.

**Study population:** In the retrospective analysis 40 patients with post-CPB vasodilatory hypotension (requirement for exogenous NE to maintain MAP >70 mm Hg and CI >2.5 L/min/m<sup>2</sup>) were included.

**Study design:** retrospective analysis

- From 145 subjects analyzed (102 male and 43 women), 40 patients fulfilled the inclusion criteria of postcardiotomy shock treated with AVP 0.1 U/min; 20 (14%) met criteria for post-CPB hypotension, with 11 cases (8%) meeting criteria for vasodilatory shock.
- Efficacy/safety measurements: Hemodynamic measurements were MAP, SVR and CI. In addition NE requirements were measured. No safety measurements were reported.
- Dose/administration: 0.1 U/min AVP. AVP infusions were instituted from 5 min to several hours after weaning from CPB (33 patients) or while the patient was still on CPB to facilitate weaning (7 patients). On identification of vasodilatory hypotension and an increasing exogenous pressor requirement, patients received AVP (Pitressin; Parke-Davis, Morris Plains, NJ) intravenously at a rate of 0.1 U/min. Subsequently CA and then AVP infusions were tapered to maintain MAP above 70 mm Hg. When hemodynamic improvement allowed discontinuation of CA agents, the AVP infusion rate was progressively decreased to 0.02 U/min and then discontinued.
- Comparators: There were no comparators

**Results:** AVP increased MAP and SVR statistically significant without affecting CI. In addition AVP decreased significantly NE requirements.

**Conclusions:** AVP induced a pressor response in this population (OHT and LVAD patients) and decreased NE requirements. From the 40 subjects analyzed only 20 met the criteria for post-CPB hypotension and from them only 11 met the criteria for postcardiotomy vasodilatory shock; the rest had cardiogenic hypotension. Since the data is not stratified by disease, it is difficult to

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

conclude about the effectiveness of AVP in postcardiotomy vasodilatory shock patients. In addition, in 7 of the subjects AVP was given before CPB.

Argenziano (1999)

**Title:** Arginine Vasopressin in the Management of Vasodilatory Hypotension After Cardiac Transplantation

**Date-Sites:** Date of study was not specified. Results were from two centers: Departments of Surgery, and Medicine, Columbia University College of Physicians, New York, NY.

**Endpoint/Variables:** Hemodynamic response (MAP) to 0.1 U/min AVP in 20 patients who developed vasodilatory hypotension after cardiac transplantation.

### **Study population**

Over 30 months, 175 adult patients underwent OHT for end-stage heart disease at our institution. After weaning from CPB, 20 of these patients (16 men and 4 women) met criteria for post-bypass vasodilatory hypotension.

**Study design:** This is a retrospective study that analyzed 20 OHT patients with vasodilatory hypotension (MAP less than 70 mmHg, CI greater than 2.5 L/min/m<sup>2</sup>, and exogenous NE requirements).

Baseline characteristics: MAP of 60 ± 15 mmHg, SVR (SVR) of 836 ± 264 dyne-sec/cm<sup>5</sup>, CI of 3.0 ± 0.5 L/min/m<sup>2</sup>, and exogenous NE requirement of 15.1 ± 13.8 µg/min. Most common concomitant medications were: 50 % of the patients had preoperative ACEI and 55% were under diuretics.

Measurements were recorded during weaning from CPB in 4 patients, immediately after weaning in 10 patients, and between 2 and 4 h after weaning in 6 patients.

Hemodynamic measurements were MAP, CVP, SVR and CI.

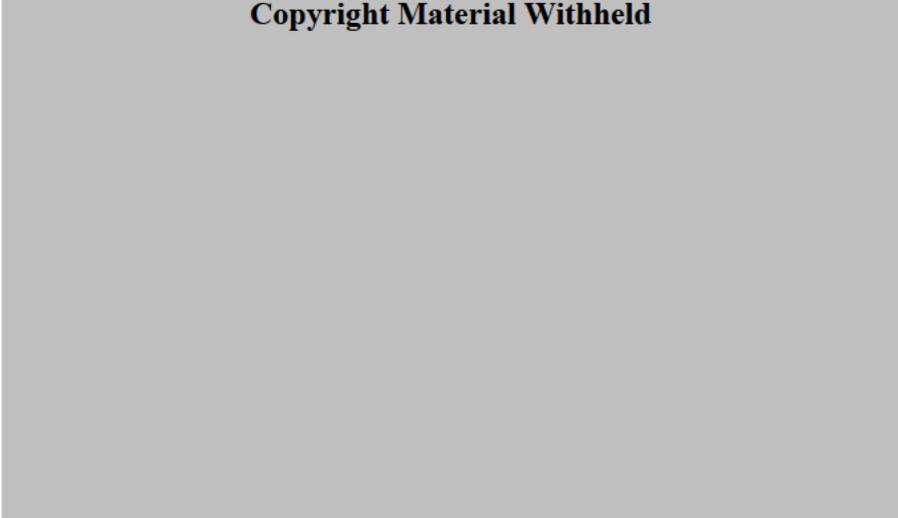
- Safety: measurements were not pre-specified
- Dose/administration: AVP (0.1U/min) was administered as infusion from 10 to 240 min after weaning from CPB. Duration of AVP infusion ranged from 2 h to 3 days,
- Comparators: AVP data were not compared to other treatments, were compared to baseline values.

### **Results**

AVP increased significantly MAP and SVR and decreased NE requirements.

**Table 21- Vasopressin effects on hemodynamics and NE requirements  
(Argenziano 1999)**

Copyright Material Withheld



The authors reported that the following AEs were not reported: episodes of malignant hypertension, mesenteric ischemia, or peripheral ischemia in the postoperative period. There were no significant changes in the mean serum creatinine level ( $1.7 \pm 0.2$  mg/dl) or serum osmolarity ( $286 \pm 4$  mOsm) on first postoperative day. There was one perioperative death, occurring on postoperative Day 21, due to hemorrhagic shock and multisystem failure, no further information is available.

**Conclusions:** The analysis showed that AVP (0.1 U/min) induced an increase over baseline of the following hemodynamic parameters in a statistically significant manner: MAP, CVP and SVR. In addition a statistically significant decrease in NE requirements in these patients was reported. AVP did not affect CI.

This study is retrospective and therefore bias cannot be excluded. There is no comparator to confirm that the effect was treatment related.

Dunser (2002)

**Title:** Cardiac performance during vasopressin infusion in post-cardiotomy shock

**Date-place:** All medical records, between January 1998 and 2001, were reviewed for patients with CA-resistant post-cardiotomy shock who were treated with a continuous IV infusion of AVP.

This study retrospectively analyzed the effects of continuous AVP infusion on cardiac performance, biomarkers of myocardial ischemia, and systemic hemodynamics. All were postcardiotomy shock patients. CA-resistant shock was defined as a failing effect of a stepwise increase of NE of  $0.2 \mu\text{g}/\text{kg}/\text{min}$  over a 2-h period to keep MAP above 60 mmHg.

**Study design:** retrospective study

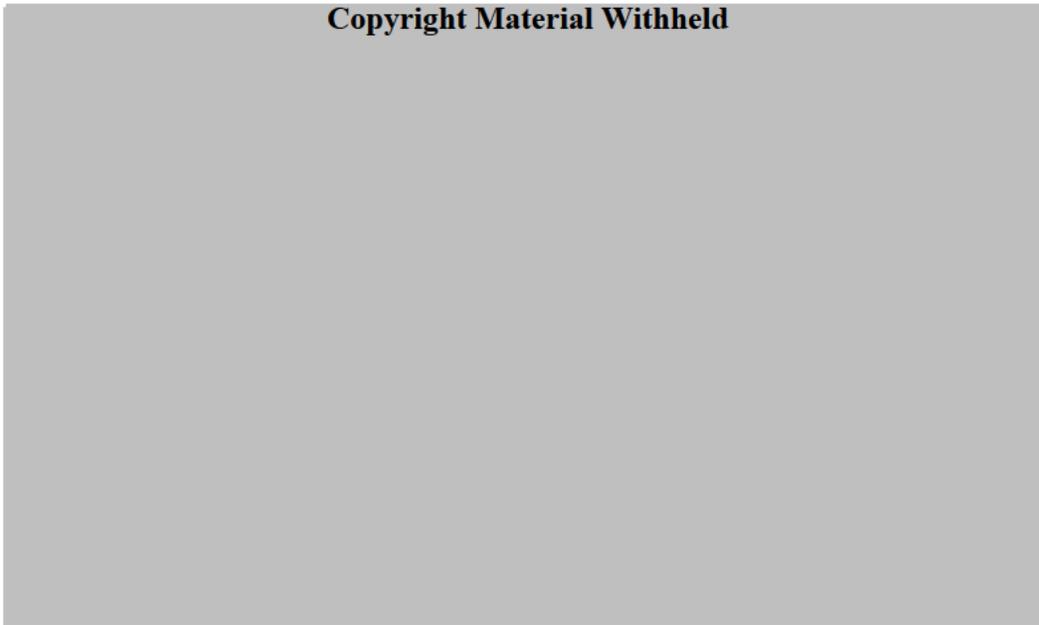
- Forty-one patients (30 males and 11 females) met the criteria for post-cardiotomy CA-resistant vasodilatory shock.
- Hemodynamic data including HR, MAP, CVP, MPAP as well as milrinone and NE requirements were recorded before and 1, 4, 12, 24, and 48 h after start of continuous AVP infusion. Pulmonary artery catheter measurements including CO, CI, SVI, and PCWP were measured before and 1–3, 4–8, 12–16, 24±5, and 48±5 h after start of AVP infusion. LVSWI, RVSWI, SVR, and PVR were calculated according to standard hemodynamic formulas.
- Safety measurements: Postoperative new-onset TA defined as a non-sinus rhythm exceeding 100 bpm were recorded by continuous ECG-monitoring on the bedside screen and noted in the patients' protocols. A 12-lead ECG was performed daily and in case of new-onset TA.
- Dose/administration: AVP infusion was given continuously with doses ranging from 4 U/h (0.067 U/min) to 6 U/h (0.1 U/min).
- Comparators: there were no comparators in this analysis

**Results**

AVP induced a statistically significant decrease in HR and a significant rise in MAP and SVR. There were no significant changes in CI and SVI during continuous AVP infusion. During the observation period milrinone and NE requirements significantly decreased by 17.5% and 54.9%, respectively. There were no changes in CVP, MPAP, PCWP, CO, RVSWI, and PVR during the observation period.

**Table 22-Cardiac parameters and vasopressor doses of study patients (Dunser 2002)**

**Copyright Material Withheld**



**Conclusion:** AVP caused a statistically significant rise in MAP and SVR. A statistically significant decrease in NE requirements was reported during AVP infusion. AVP infusion did not decrease myocardial performance, as assessed by CI and SVI in CA-resistant postcardiotomy shock. A significant difference in the incidence of new-onset TA between AVP and NE arm was observed in this study conducted in 48 patients with CA-resistant vasodilatory shock. Two of 24 patients (8.3%) receiving AVP developed new-onset tachycardic atrial fibrillation, whereas 14 of 24 NE patients (54.3%) experienced new-onset atrial fibrillation during the observation period ( $P < 0.001$ ).

Morales (2000)

**Title:** Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock.

**Date–location–center:** The medical records of the 102 patients (16 % women) receiving LVADs at Columbia-Presbyterian Medical Center from January 1995 to August 1998 were reviewed

Fifty patients receiving LVAD were eligible for study based on a history of AVP administration in the operating room or ICU within 24 h of implantation. Seven of these subjects participated in the prospective study by Argenziano 1997. MAP and SVR were the hemodynamic measurements.

**Study design:** retrospective study.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

- All hemodynamic data and IV drug doses were recorded 15 min before and 15 min after initiation of AVP.
- Dose/administration: AVP 0.067 U/min to 0.1 U/min
- Comparators: there were no comparators.

## Results

A statistically significant increase in MAP and SVR and no effect on PAP was reported with AVP, mean dose was  $0.09 \pm 0.05$  U/min (dose range was 0.067 to 0.1 U/min). A modest decrease in the NE requirements was reported.

Ventricular arrhythmias were observed and there were no reports of ischemic bowels.

**Conclusions:** AVP increased MAP and SVR. No conclusions can be made from the AEs reported because of the lack of comparator.

## Studies conducted in patients undergoing elective cardiovascular surgery.

Hasija (2010)

**Title:** Prophylactic Vasopressin in Patients Receiving the Angiotensin-Converting Enzyme Inhibitor Ramipril Undergoing CABG Surgery

**Dates of study:** Between April and October 2008.

**Objective:** to assess the efficacy of prophylactic AVP infusion on hemodynamic stability and vasoactive drug requirements in patients treated with ACEI undergoing CABG surgery.

**Study population:** Patients included were those undergoing elective primary CABG surgery on CPB and receiving the ACE inhibitor ramipril for at least the past 6 weeks. Patients with concomitant valvular disease, congestive heart failure, renal dysfunction (serum creatinine  $\geq 2.0$  mg/dL), hepatic dysfunction (serum bilirubin  $\geq 3.0$  mg/dL), severe lung disease, peripheral vascular disease, history of stroke, hypersensitivity to AVP, and those undergoing emergency surgery or reoperation were excluded from the study.

**Study design:** A prospective, randomized, double-blinded, single-center clinical study.

- Sample size: 47 patients
- Duration of follow-up: Hemodynamic parameters and vasoactive drug requirements were recorded for 3 days postoperatively.
- Efficacy/safety measurements: Hemodynamic parameters recorded included HR, MAP, CVP, MPAP, PCWP, CI, and SVR. Of these, MPAP, PCWP, CI, and SVR were recorded only in the operating room.
- Dose/administration: AVP infusion (0.03 U/min) was administered from the onset of rewarming until the hemodynamics was stable without vasopressor agents.
- Blinded/randomized: Using computer-generated tables, patients were randomly allocated to 1 of 3 groups: patients who discontinued ramipril 24 h before surgery (group A), patients who continued ramipril until the morning of surgery (group B),

and patients who continued ramipril until the morning of surgery and received AVP infusion intra-operatively (group C).

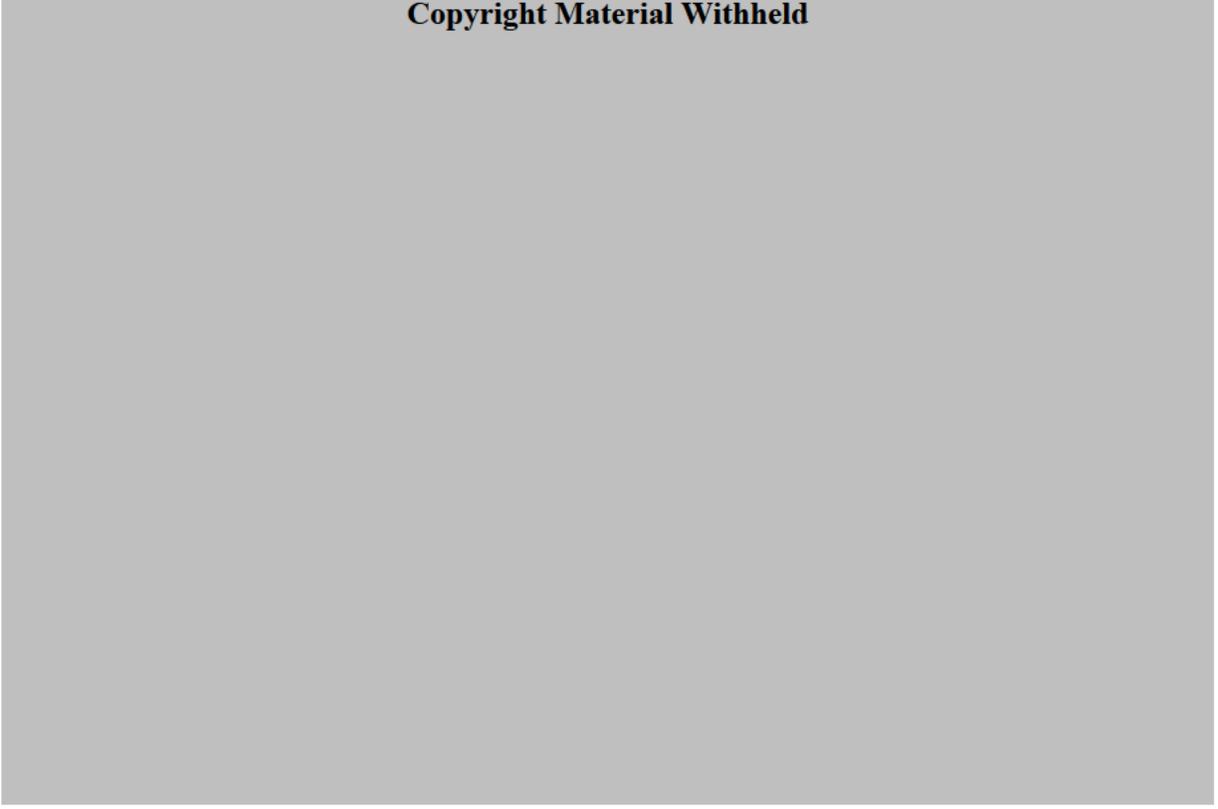
- Comparators: Group A: patients who discontinued ACEI before surgery (n=16, 15 males and 1 female), Group B: Patients under ACEI during the procedure (n=16, 16 males). Group C: patients with ACEI+ AVP 0.03 U/min (n=15, 13 males and 2 females).

### Results

In group B (subjects under ACEI treated with saline) there was a decrease in MAP and SVR post-CPB compared to baseline and values were lower than in group C (subjects under ACEI treated with AVP) post-CPB.

**Table 23- Prophylactic effect of Vasopressin on Vasodilatory Shock post-CPB (Hasija 2010)**

Copyright Material Withheld



### Conclusions

An infusion with AVP 20 min before CPB and during CPB may prevent hypotension post-CPB in subjects receiving ACEI.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

It is not clear if the hypotension linked to pharmacological ACE inhibition is comparable to vasodilatory shock developed after CPB without ACE inhibition.

Morales (2003)

**Title of the study:** A Double-Blind Randomized Trial: Prophylactic Vasopressin Reduces Hypotension After Cardiopulmonary Bypass

**Date and centers:** The study was conducted in one center. Study date was not provided

**Hypothesis:** In patients receiving ACE inhibition, initiation of AVP before CPB would diminishes post-CPB hypotension and catecholamine use.

**Study population:** Subjects undergoing CABG and/or valvular surgery and on preoperative ACE inhibitors for > 2 weeks. Patients who manifested hypovolemic or cardiogenic shock (CI less than 1.8 L/ min/ m<sup>2</sup> 15 min after CPB) were to be removed from the study.

**Study design:** double-blinded randomized placebo-controlled trial

- Cardiac surgical patients on ACE inhibitor therapy were randomized to receive an AVP dose of 0.03 U/min (n=13) or an equal volume of normal saline (n=14) starting 20 min before CPB. Study drug was maintained for a maximum of 72 h or until the patient was stable off all CA vasopressors and being discharged from the ICU.
- Efficacy measurements: MAP, NE requirements and period under CA, number of hypotensive episodes and length of stay at the intensive care unit. Hemodynamic data were recorded continuously during administration of the infusions; CO was measured per routine with a definite measurement at 15 min after CPB ended to determine continued participation in the protocol
- Safety measurements: Authors do not pre-specify AEs of interest to be monitored during the study, but report safety results.
- Dose/administration 0.03 U/min AVP. Plasma AVP levels were determined at baseline and posttreatment.

## Results

### Subjects

Thirty three subjects entered the study; 16 patients were randomized to placebo and 17 to AVP. Two patients in the placebo group could not be weaned from CPB because of intractable vasodilatory shock and received AVP, the standard of care in the institution. Four patients in the AVP group were withdrawn from the study; subjects were discontinued because study drug administration was inadvertently stopped during the first 6 h, out of protocol and therefore were excluded from the analysis. The remaining 27 patients were analyzed.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

### Baseline

The AVP group did not differ significantly from the placebo group with respect to age, sex, CPB time, or preoperative left ventricular EF.

The number of patients in the AVP and placebo group taking each specific ACE inhibitors were respectively: enalapril (5, 2) quinapril (3, 1), lisinopril (4,5) and captopril (2,2). In the placebo group patients had also been taking fosinopril (1), benazepril (1), and other ACE inhibitor (1). No unbalance was observed between groups in the type of cardiac procedures that patients underwent: CABG, valve procedure only and combined revascularization and valve procedure.

### Hemodynamic

The hemodynamic baseline data of the first 5 patients were not collected. The administration of AVP pre-CPB did not significantly change MAP, MPAP, SPAP, or diastolic pulmonary artery pressure, compared to placebo: MAP:  $80 \pm 12$  to  $78 \pm 11$  mm Hg,  $p = \text{NS}$ ; MPAP:  $22 \pm 8$  to  $23 \pm 8$  mm Hg,  $p = \text{NS}$ ; SPAP:  $34 \pm 6$  to  $33 \pm 8$  mm Hg,  $p = \text{NS}$ , or diastolic pulmonary artery pressure ( $16 \pm 7$  to  $18 \pm 8$  mmHg,  $p = \text{NS}$ ).

Peak NE doses were significantly higher in the placebo group than in the AVP group ( $7.3 \pm 3.5$  vs  $4.6 \pm 2.5$   $\mu\text{g}/\text{min}$ ,  $p = 0.03$ ), as was the duration of CA use ( $11 \pm 7$  versus  $5 \pm 6$  h,  $p = 0.03$ ) and the number of hypotensive episodes ( $4 \pm 2$  versus  $1 \pm 1$ ,  $p < 0.01$ ). The AVP group also had significantly shorter intubation time ( $1.0 \pm 0.4$  versus  $1.4 \pm 0.5$  days,  $p = 0.02$ ) and length of ICU stay ( $1.2 \pm 0.4$  versus  $2.1 \pm 1.4$  days,  $p = 0.03$ ).

### Safety

Two complications occurred in each group: acute renal insufficiency and right heart failure in the AVP group and acute renal insufficiency and a lethal hemorrhage in the normal saline group. No instances of postoperative myocardial infarction, hepatic insufficiency, intestinal infarction, limb digit ischemia, or stroke were noted in either group.

### **Conclusions**

This study intended to show that a low dose of AVP given pre-CPB in patients pretreated with ACEI prevent the hypotension expected in patients pretreated with ACEI. However, this study has several weaknesses that make it impossible to draw any conclusions:

No significant post-CPB MAP changes were found between groups (post CPB MAP values in patients treated with placebo should have been much lower than the AVP treated group). The study reports a statistically significant decrease in NE requirements which does not appear as clinically meaningful ( $7.3 \pm 3.5$  versus  $4.6 \pm 2.5$   $\mu\text{g}/\text{min}$ ,  $p = 0.03$ ).

It is not clear if the hypotension linked to pharmacological ACE inhibition is comparable to vasodilatory shock developed after CPB without ACE inhibition.

Papadopoulos (2010)

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Title:** Perioperative infusion of low- dose of vasopressin for prevention and management of vasodilatory vasoplegic syndrome in patients undergoing CABG-A double-blind randomized study

**Date:** A total of 50 patients aged 32 to 81 were operated between January 2003 and December 2005.

**Objective:** The aim of the study was to investigate the effects of prophylactic administration of low-dose of AVP (of 0.03 U/min for 4 h), on the patients' hemodynamics, on the incidence of vasodilatory shock, and on urine output and blood loss, for the 1<sup>st</sup> day after the operation.

**Subjects:** patients undergoing elective CABG: EF was between 30-40%. Patients were receiving ACE inhibitors, at least for four weeks preoperatively.

Patients were excluded, according to the following criteria:

1. EF less than 30%,
2. In shock or critical hemodynamic state
3. Confirmed hepatic, and/or renal, and/or thyroid, and/or adrenal disease,
5. Significant peripheral obstructive arteriopathy,
6. Documented pulmonary hypertension, expressed by systolic pulmonary pressure >30-35 mm Hg, and
7. Chronic obstructive pulmonary disease, confirmed by preoperative spirometry, thorax X-rays and blood gas analysis.

**Study design:** double-blinded placebo-controlled.

- Sample size: 50 subjects (9 females and 41 males) were studied, 25 in the AVP group and 25 in the saline group.
- Efficacy/safety measurements: MAP, CVP, SVR, EF, HR, MPAP, CI and PVR were performed before, during, and after the operation.  
Other data collected: The requirements of CA support, the urine-output, the blood-loss, and the requirements in blood, plasma and platelets for the first 24 h were included in the data collected.
- Dose/administration: AVP 0.03 U/min infusion started 20 min before beginning the CPB and was continued throughout the operation for the next 4 h after termination of the CPB. In group B, a solution of normal saline was administered in the same dose, way, and duration. Both solutions were prepared by a nurse. Ten minutes before termination of the CPB, a solution of NE, at a dose of 0.03 µg/Kg/min was routinely administered (in continuous IV infusion), and it was individually increased up to 0.05 µg/Kg/min during the next 24 h until extubation, depending on the hemodynamic state of each patient. An additional dose of EPI of 0.01-0.03 µg/Kg/min was selectively infused in patients to whom the above dose of NE was insufficient in order to restore a normal CO, whereas in every patient with vasodilatory shock.
- .

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

- Arms: Group A, infused with 0.03 U/min AVP and group B, infused with normal saline intraoperatively and for the 4 postoperative hours.

## Results

Patient demographic characteristics did not differ between groups.

Instead of tabulated data, the authors provided plots for hemodynamic parameters which are neither explained nor quoted or discussed in the text.

**Conclusions:** This study was conducted in patients undergoing elective cardiac surgery, who at study entry, were not in vasodilatory shock. The authors did not report the hemodynamic findings. Another limitation is that in both groups a NE infusion was started 10 min before ending the CPB and up titrated. In addition, EPI was added on top of NE depending on the hemodynamic status of each patient. All these limitations make data quite difficult to interpret.

### 9.1.3. Vasodilatory Postcardiotomy Shock (Pediatric)

Alten (2012)

**Title:** Early initiation of arginine vasopressin infusion in neonates after complex cardiac surgery

**Design:** Single center retrospective cohort study of 37 consecutive neonates.

**Study subjects:** from March 2010 to September 2010, 19 consecutive patients undergoing the Norwood procedure (NP, n = 13) or arterial switch operation (ASO, n = 6) were treated with an AVP infusion (AVP+). Data from these patients were compared to 18 consecutive patients, from December 2008 to March 2010 (11 NP and 7 ASO), that did not receive AVP infusion (AVP-).

**Dosing:** starting dose 0.0003 U/kg/min (range 0.00008 to 0.001 U/kg/ min); subjects were under background medication (vasopressors and fluid).

#### Results:

**Safety-** No episodes of necrotizing enterocolitis were reported. All surviving patients tolerated enteral feeds

The authors concluded that low-dose AVP infusion initiated in the operating room after complex neonatal cardiac surgery was associated with decreased fluid resuscitation and CA requirements in the first 24 postoperative hours. Groups AVP- and AVP+ had similar MAP, and all other hemodynamic variables including HR, CVP, urine output and mean lactate ( 3.6 in AVP+ and 3.4 mmol/L in AVP- at 24 h)

**Conclusion:** Low-dose AVP initiated in the operating room after complex neonatal cardiac surgery was associated with decreased fluid resuscitation and CA requirements in the first 24 postoperative hours. Major limitations are that study subjects were not in vasodilatory shock, and there was no control group, therefore there is not enough information to conclude about safety and efficacy in these patients.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Lechner (2007)

**Title:** Arginine-vasopressin in neonates with vasodilatory shock after cardiopulmonary bypass

**Design:** retrospective study. Results analyzed were extracted from a database, from March 2003 through December 2005.

**Subjects:** the analysis was conducted in a series of 172 neonates (age range 1-28 days) that had undergone open-heart surgery; 17 patients developed vasopressor-resistant hypotension and were treated with AVP. The criteria for starting AVP was low CO status with hypotension, which was defined as SBP below 55 mmHg refractory to fluid replacement and administration of high doses of DA, EPI and NE with decreasing urine output or increasing serum lactate levels.

**Dosing:** AVP was started at median 0.0001 U/kg/min (range 0.00005–0.0002) and titrated to effect (SBP > 65 mmHg) to a maximum of median 0.0003 U/kg/min (range 0.0001–0.001).

Vasopressor and inotropes: DA (n = 16), dobutamine (n = 1), EPI (n = 16), and NE (n = 17) were administered prior to starting AVP.

**Results:** SBP increased significantly in all patients, from a mean of  $49 \pm 8$  to  $69 \pm 7$  mm Hg ( $p < 0.00001$ ). Findings include a statistically significant decrease in vasopressor requirements.

The article reports that no subject showed clinical signs of peripheral ischemia or reduced organ perfusion throughout continuous infusion of AVP.

No patient developed signs of necrotizing enterocolitis due to mesenteric ischemia like distension of the intestinal loops in abdominal radiography or air in the portal system on ultrasound examination. Enteral nutrition was well tolerated in all survivors. No cutaneous ischemia was observed.

Four patients died, 2 of them during AVP infusion; both patients had hypoplastic left heart syndrome: one patient died 42 hours post-operatively after prolonged hypoxemia and the second had cardiac arrest on post-operative Day 4, when AVP was almost weaned.

**Conclusions:** AVP increases SBP; the effect was statistically significant. AVP decreased vasopressor requirements. Major drawbacks are the retrospective nature of the analysis, as bias cannot be excluded, and the low number of subjects. Neither peripheral or mesenteric ischemia nor signs of decreased organ perfusion were reported.

Rosenzweig (1999)

**Title:** Intravenous Arginine-Vasopressin in Children With Vasodilatory Shock After Cardiac Surgery

**Design:** Retrospective study

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

**Subjects:** 11 children (5 males, 6 females, median age of 35 days (3 days to 15 years) with vasodilatory shock after CPB refractory to standard vasopressors. Ten patients had congenital heart defects and 1 had dilated cardiomyopathy.

**Dosing:** Children received AVP as an IV infusion with a starting dose adjusted for weight (range from 0.0003 to 0.002 U/kg/min) for a mean of  $71 \pm 46$  h (6–144 h). Cardiopressors and inotropes, including dobutamine (n=10), EPI (n=8), milrinone (n=7), and DA (n=4), were given before AVP.

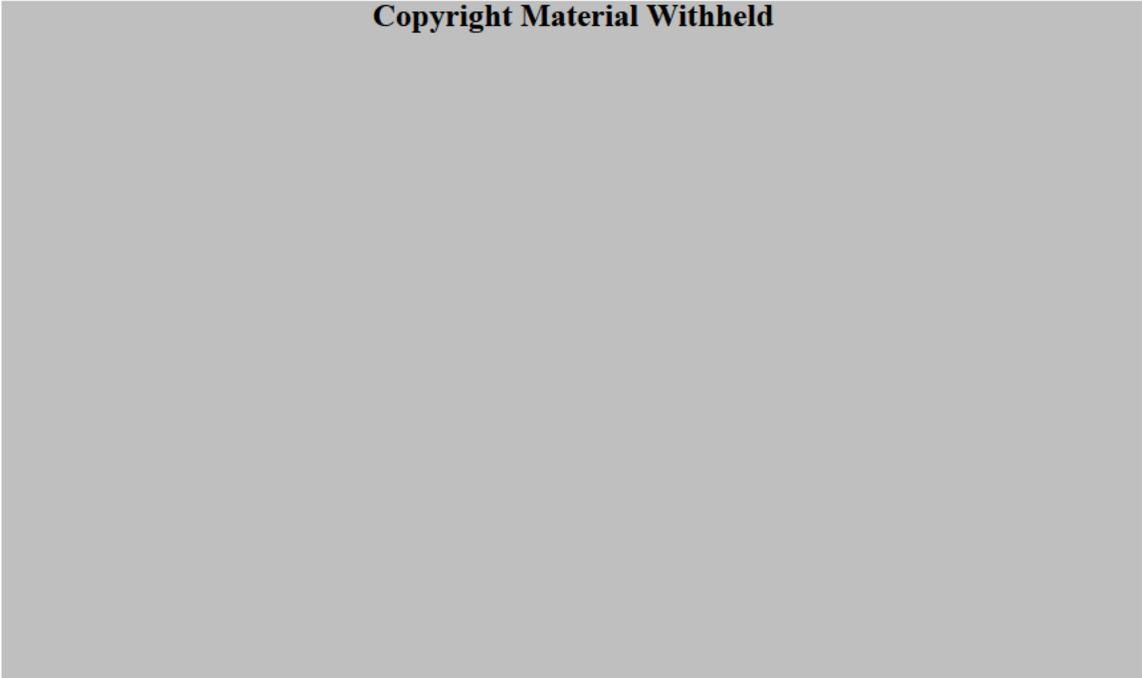
**Statistics:** Data are reported as mean  $\pm$  SD. Paired variables were analyzed by the Student paired t test or the paired sign test when appropriate

**Results:**

As seen in the table below, 5 were females and 6 were males, with ages varying from 4 days to 15 years. Nine patients had vasodilatory shock and 2 cardiogenic shock.

**Table 24- Pediatric Patients Profile (Rosenzweig, 1999)**

Copyright Material Withheld



At baseline, the SBP was low and rose 34% with administration of AVP from  $65 \pm 14$  to  $87 \pm 17$  mm Hg ( $P < 0.0001$ ; n=11). DBP increased 31%, from  $35 \pm 11$  to  $46 \pm 13$  mm Hg ( $P < 0.005$ ; n=11), and MAP increased 31%, from  $45 \pm 11$  to  $59 \pm 11$  mm Hg ( $P < 0.0005$ ; n=11).

The mean doses of pressors at baseline and follow-up were dobutamine  $10 \pm 3$  versus  $8 \pm 5$   $\mu\text{g}/\text{kg}/\text{min}$  (n=10), EPI  $0.36 \pm 0.49$  versus  $0.14 \pm 0.18$   $\mu\text{g}/\text{kg}/\text{min}$  (n=9), DA  $7.0 \pm 2.9$  versus  $6.0 \pm 3.1$   $\mu\text{g}/\text{kg}/\text{min}$  (n=4), and milrinone  $0.5 \pm 0.1$  versus  $0.4 \pm 0.2$   $\mu\text{g}/\text{kg}/\text{min}$  (n=57). No significant change over baseline doses was observed.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Indexes of organ perfusion, including urine output and sodium bicarbonate scores, were not significantly changed during the first 24 and 8 h, respectively, on AVP infusion, suggesting no adverse effect on renal perfusion.

**Safety:** There were no episodes of peripheral vasoconstriction or cyanosis that required discontinuation of AVP.

Early outcome (24 h) was favorable in the 9 critically ill patients. Of the 9 patients with vasodilatory shock, 1 was taken off LVAD and subsequently underwent successful heart transplantation (#7), 1 avoided LVAD placement as a bridge to heart transplantation (#8), and 5 were successfully weaned from CPB. The 2 patients with cardiogenic shock (poor left ventricular function by echocardiogram before initiation of AVP) died at 6 h (#10) and 6 days (#11) after initiation of continuous AVP, despite transient improvements in systemic arterial BP.

**Conclusions:** AVP increases DBP and SBP and the effect is statistically significant. AVP did not reduce significantly vasopressors requirements. All vasodilatory shock patients survived at 2 weeks postsurgery. However, since there is no comparator this is difficult to interpret.

Major drawbacks are the retrospective nature of the analysis that cannot exclude bias and the low number of subjects studied (11 children, 9 with vasodilatory shock) with a broad age range (median age of 35 days, range: 3 days to 15 years).

#### 9.1.4. Vasodilatory Septic Shock (Pediatric)

Choong (2009)

**Title:** Vasopressin in Pediatric Vasodilatory Shock A Multicenter Randomized Controlled Trial

**Date and site:** This study was conducted between August 2003 and April 2007 in seven Canadian Pediatric Critical Care Units

**Primary outcome:** time to vasoactive-free hemodynamic stability.

**Secondary outcome:** mortality, organ-failure-free days, length of critical care unit stay, and adverse events.

**Study population:**

**Inclusion:** (1) volume resuscitation of at least 40 ml/kg; (2) at least 10 mg/kg/min of dopamine or any dose of EPI, NE, or PHE; and (3) clinical evidence of vasodilatory shock (defined as a DBP of less than half SBP and two of the following: tachycardia, warm extremities, or flash capillary refill).

**Exclusion:** death anticipated within 24 h or a lack of commitment to life support, use of AVP or its analogs in the previous 24 h, known history of vasospastic diathesis, concurrent use of intravenous vasodilator agents (sodium nitroprusside or phenoxybenzamine), hypersensitivity to AVP, severe hyponatremia (serum sodium less

than 125 mM despite water restriction), known diagnosis of diabetes insipidus or syndrome of inappropriate antidiuretic hormone secretion, and pregnancy. Patients were also excluded if a low CI of equal to or less than 2.5 L/min/m<sup>2</sup> after fluid resuscitation was measured by pulmonary artery catheter or echocardiography.

Study design: randomized, double-blind, controlled trial

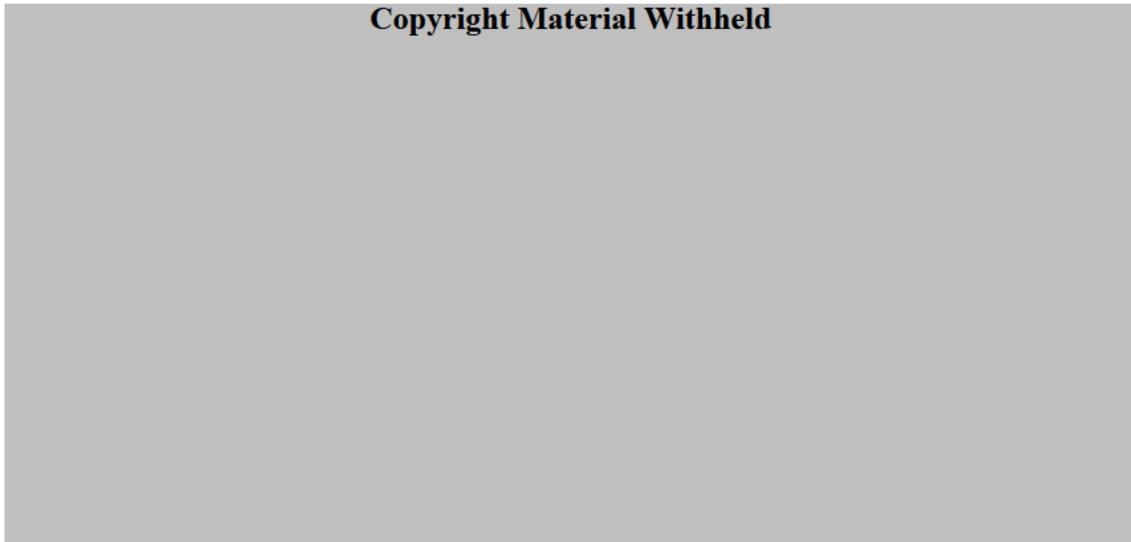
- Sample size: 69 patients were required to achieve 90% power to detect a hazard ratio of 3 and a significance level of 5% using Lakatos' formula for survival analysis. This sample size calculation accounted for a 34% mortality rate and a 7% possible dropout or postrandomization exclusion rate. 65 subjects were included in the analysis.
- Efficacy: the time from study drug initiation to the time when all vasoactive agents were successfully discontinued
- Safety measurements: adverse events and serious adverse events were reported.
- Dose/administration: AVP starting dose was 0.0005 U/kg/min. The study drug was administered in addition to the open-label vasoactive infusions that patients were already receiving at baseline and titrated every 5 min up to 0.002 U/kg/min (0.05 U/min maximum total dose) to maintain a target MAP for age. Once the patient achieved their target MAP for at least 4 h without escalation in hemodynamic support, accompanied by clinical evidence of adequate end-organ perfusion, open-label vasoactive infusions were weaned in accordance with the recommended study guidelines. The study drug was weaned after both target MAP and end-organ perfusion were maintained without open-label infusions for at least 4 h.
- Comparators: AVP+ open-label vasopressor, saline + open label vasopressor

## Results

Sixty-five of 69 children (94%) who were randomized received study drug (33 AVP, 32 under placebo) and were included in the analysis. The median dose of AVP use during the study was 0.0011 U/kg/min (interquartile range [IQR] 0.0007–0.0018) or 0.04 U/min. Cause of vasodilatory shock differed between arms i.e, placebo arm has a more homogenous population with 88 % of the participants with vasodilatory septic shock vs 68 % in the AVP group. The AVP group had 3 (8.6%) patients with postcardiotomy vasodilatory shock vs 0% in the placebo group and 14.3 % of the patients in the AVP group had vasodilatory shock from undetermined cause vs 8.8% in the placebo group. Baseline AVP levels were low in both groups (3.8 pg/ml), and baseline cortisol levels were markedly elevated in both groups.

**Table 25- Baseline characteristics of pediatric patients (Choong 2009)**

**Copyright Material Withheld**



There was no significant difference in the primary outcome between the two study groups. The median time to achieve hemodynamic stability was 49.7 h in the AVP group and 47.1 h in the placebo group ( $P = 0.85$ ). The vasoactive free, organ failure-free and ventilator-free days, organ dysfunction scores, and the length of pediatric critical care unit stay were not significantly different between the experimental and control groups.

There was a significant increase in MAP 1 h after infusion of AVP compared to baseline. The effect was statistically significantly different from placebo.

There were 10 (30%) deaths in the AVP group, compared with five deaths (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval [CI], 0.75–5.05;  $P = 0.24$ ). Most common cause of death in the two groups was treatment failure i.e, refractory shock and multisystem organ dysfunction syndrome. Some of the deaths in the AVP group could be related to the underlying condition rather than AVP administration and took place days after AVP discontinuation (see section 7.3.1. Table 10).

Two cases of digital ischemia were reported in the AVP group, no digital ischemic episodes were reported with open-label vasopressors + saline (Table 8).

**Conclusions:**

This is a double-blind controlled study. Subjects received blinded study drug or placebo; therefore chances of bias are minimal. Study subjects were children with vasodilatory shock that were randomized to low-dose AVP (0.0005–0.002 U/kg/min) or placebo in addition to open-label vasoactive agents.

Despite the fact that the study failed to demonstrate the primary endpoint, low doses of AVP were shown to increase MAP 1 h after infusion.

Clinical Review  
Mónica L. Fiszman, M.D., Ph.D.  
NDA # 204-485  
Vasopressin

Although the majority of participants were septic shock patients, postcardiotomy shock patients were 8.6% of the total in the AVP arm, shock of undetermined cause were 14 % and 8.8% in the AVP and placebo group respectively.

It is important to note that two cases of digital ischemia were reported with low dose of AVP in this study. Therefore doses to develop digital ischemia are similar to those in adults (Russell 2008).

There was a trend toward increased mortality. However, the five cases reported in the placebo group were treatment failure and 6 from the 10 deaths in the AVP as well. The rest of the cases (n=4) reported in the AVP group were confounded by underlying conditions rather than by AVP exposure. Mesenteric ischemia is an expected AVP serious AE however, in the fatal case reported subject had post-radiation enterocolitis that could have had precipitated the fatal outcome. Moreover, the role of background medications in these deaths is unknown. The clinical reviewer concludes that further studies should be conducted to understand the AVP safety profile in children.

## **9.2 Labeling Recommendations**

Labeling recommendations will follow separately.

## **9.3 Advisory Committee Meeting**

No advisory committee meeting was scheduled.

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

/s/  
-----

MONICA L FISZMAN  
05/25/2013



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2  Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		x		
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			x	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?			x	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?			x	
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_\_\_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

---

Reviewing Medical Officer Date

---

Clinical Team Leader Date

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

/s/  
-----

MONICA L FISZMAN  
12/04/2012