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APPLICATION NUMBER:

212593Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2) NDA
Application Number(s)	212593
Priority or Standard	Standard
Submit Date(s)	March 29, 2019
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PDUFA Goal Date	January 29, 2020
Division/Office	Division of Cardiovascular and Renal Products / OND
Reviewer Name(s)	Charu Gandotra MD
Review Completion Date	November 29, 2019
Established/Proper Name	Vasopressin
(Proposed) Trade Name	Vasopressin Injection, USP
Applicant	American Regent, Inc.
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	Intravenous infusion titrated (b) (4) Post-cardiotomy shock: 0.03 to 0.1 units/minute Septic shock: 0.01 to 0.07 units/minute
Applicant Proposed Indication(s)/Population(s)	Increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines

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1. Executive Summary

On March 29, 2019, American Regent (AR), Inc. submitted a 505(b)(2) New Drug Application for Vasopressin Injection, USP, 20 units/mL single dose vial, to be administered as an infusion for treatment of patients with vasodilatory shock who remain hypotensive despite fluids and catecholamines. AR proposed to rely on FDA's findings of safety and efficacy for Vasostrict, the Reference Listed Drug (RLD) for Vasopressin. Vasostrict (vasopressin) (NDA 204485) manufactured by Par Pharmaceutical Companies, Inc., Spring Valley, New York was approved by FDA on April 17, 2014, to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. Approved dose for Vasostrict is 0.03 to 0.1 units/minute to treat post-cardiotomy shock, and 0.01 to 0.07 units/minute to treat septic shock.

NDA 212593 is based on literature published between April 14, 2014 (date of Vasostrict approval) and September 17, 2018, to identify any new data that may be inconsistent with FDA's previous findings of safety and efficacy for Vasostrict. The applicant submitted 35 studies - 11 trials to support efficacy and safety, 5 studies to support safety, 4 systematic literature reviews, and 15 case reports.

For efficacy, the clinical review focused on 2 prospective, randomized trials that evaluated the use of vasopressin (AVP) on background therapy with norepinephrine (NE) and provided data on change in mean arterial pressure (MAP). For safety, the clinical review focused on published literature, and information from the applicant's pharmacovigilance database and the FDA adverse event reporting system. In summary, the published literature continues to support FDA's previous findings of safety and efficacy for AVP. A new safety signal of development of transient diabetes insipidus (DI) after discontinuation of AVP infusion was identified based on case reports. Most cases of DI resolved within 24 hours with treatment comprised of intravenous fluids, re-initiation of AVP infusion, and/or Desmopressin. This finding does not change the overall benefit-risk profile for AVP.

In conclusion, from a clinical perspective, the application may be approved. The potential for the development of transient DI after cessation of AVP infusion should be included in the label for Vasopressin Injection, USP and the label for Vasostrict should be accordingly revised.

Addendum July 7, 2020: The applicant re-submitted NDA 212593 on June 4, 2020 as a Class 1 resubmission with administrative updates only. No additional clinical data were submitted. No changes to the Clinical Review Document in DARRTS dated December 2, 2019 were made except the addition of the following statement: As this NDA relied on data from published literature, financial certification and disclosure documents are not applicable.

1. Therapeutic Context

Analysis of Condition

Vasodilatory shock (VS) is characterized by hypotension due to decreased systemic vascular resistance, tissue hypoperfusion leading to inadequate cellular oxygen utilization, increase in levels of lactate, and organ failure. VS comprises of ≥ 66% of all types of shock.[1] Septic shock is the most common etiology of VS. The true incidence of sepsis and septic shock is not known. The frequency of septic shock in patients admitted to intensive care unit (ICU) is estimated at 10.4%[2]. Other causes of VS include anaphylaxis, neurogenic shock, cardiovascular surgery requiring cardiopulmonary bypass, etc.[3] Shock is associated with a high mortality rate of 30 to 50%.[2]

Analysis of Current Treatment Options

The recommended treatment for VS includes intravenous (IV) administration of fluids and vasopressors to achieve a target MAP of ≥ 65 mm Hg.[3] Adjunctive therapy with IV inotropic agents and hydrocortisone (HCT)[4] may be needed in refractory cases of VS. NE is the first-line vasopressor indicated to treat VS. AVP or epinephrine or angiotensin II can be added to NE to increase MAP, or AVP can be added to reduce the dose of NE. In advanced stages of VS, adrenergic hyposensitivity leading to a loss of catecholamine pressor effect has been observed.[5]

In rare circumstances, dopamine can be used as an alternative to NE, for example in patients with low risk for tachyarrhythmias. Dobutamine may be used in patients who have persistent hypoperfusion despite adequate fluid resuscitation and use of vasopressors[6].

Approved therapies to treat patients with hypotension in shock have not

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[1] Abril MK, Khanna AK, Kroll S, McNamara C, Handisides D, Busse LW. Regional differences in the treatment of refractory vasodilatory shock using Angiotensin II in High Output Shock (ATHOS-3) data. J Crit Care. 2018;50:188–94.

[2] Jean-Louis Vincent, Gabriel Jones, Sholto David, Elena Olariu & Kevin K. Cadwell. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Critical Care volume 23, Article number: 196 (2019).

[3] Prielipp R, et al. Cardiovascular failure and pharmacologic support after cardiac surgery. New Horizons: An official publication of the Society of Critical Care Medicine. 1999;7(4):16. PMID: NA

[4] J.C. Jentzer, S. Vallabhajosyula, A.K. Khanna, L.S. Chawla, L.W. Busse, K.B. KashaniManagement of refractory vasodilatory shock Chest, 154 (2) (2018), pp. 416-426

[5] Dunser MW, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation. 2003a;107(18):2313-9. PMID: 12732600

[6] Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

demonstrated an effect on clinical outcomes or mortality. A demonstration of efficacy to increase MAP in patients with shock has been the regulatory basis for approval, as maintenance of blood pressure is important to preserve vital organ function and allows time for disease specific intervention(s). In 2017, FDA approved angiotensin II acetate (Giapreza 2.5 mg/ml Injection, NDA 209360) to increase blood pressure in adults with septic or other distributive shock based on the demonstration of efficacy of angiotensin in raising MAP. Table 1 summarizes the currently available therapies to increase MAP.

AVP is approved as Vasostrict to treat patients with VS. AVP, also known as the antidiuretic hormone, regulates plasma osmolality and extracellular fluid volume at physiologic levels. Increase in plasma osmolality and decrease in blood pressure stimulate the release of AVP. AVP exerts it's vasopressor effect through AVP type 1 (V1) receptors in the vasculature and it's antidiuretic effect through AVP type 2 (V_2) receptors in the kidney. AVP acts as a vasoconstrictor without much antidiuretic effect only during periods of hypovolemia and hypotension.[7] In the intestinal tract, AVP increases peristaltic activity, especially of the large bowel. Hence, AVP is used to treat hypotension associated with shock and its synthetic analogue, Desmopressin is used to treat diabetes insipidus (DI). Off-label uses of AVP include treatment of cardiac arrest, prevention or relief of intestinal paresis, dispel interfering gas shadows and/or to concentrate contrast media prior to abdominal radiographic procedures.[8,9]

[7] Gordon AC, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients with Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18. PMID: 27483065

[8] Dunser MW, et al. A century of arginine vasopressin research leading to new therapeutic strategies. Anesthesiology. 2006;105(3):444-5. PMID: 16931974

[9] Treschan TA, et al. The vasopressin system: physiology and clinical strategies. Anesthesiology. 2006;105(3):599-612; quiz 39-40. PMID: 16931995

Table 1. Currently Available Treatment for the Proposed Indication of Vasodilatory Shock

Product (s) Name	Relevant Indication	Approval	Dose and Route of Administration	Mechanism of action	Key Warnings and Precautions
FDA Approved - Catecholamines					
Nor-epinephrine	Hypotension	2007	Intravenous infusion: 8 to 12 mcg/min	Beta-1 and Alpha-1 adrenergic receptor agonist	Bradycardia
Phenylephrine	Hypotension	1954	Bolus intravenous injection: 40 mcg to 200 mcg Intravenous infusion: 10 mcg/min to 35 mcg/min, titrating to effect, not to exceed 200 mcg/min	Alpha-1 adrenergic receptor agonist	Exacerbation of angina, heart failure, or pulmonary arterial hypertension Excessive peripheral and visceral vasoconstriction Severe bradycardia and decreased cardiac output Increase the need for renal replacement therapy in patients with septic shock
Dopamine	To correct hemodynamic imbalances	1983	Intravenous infusion: 2 to 50 mcg/kg/min	Dopamine, Beta-1 and Alpha-1 adrenergic receptor agonist	Ventricular arrhythmias Excessive peripheral and visceral vasoconstriction
Ephedrine	Hypotension	2016	Intravenous bolus: 5 to 10 mg as needed, not to exceed 50 mg	Alpha- and beta-adrenergic agonist	Tachyphylaxis and tolerance
Metaraminol	Hypotension	1999	Intramuscular or subcutaneous injection: 2 to 10 mg Intravenous infusion: 15 to 100 mg	Alpha-1 adrenergic receptor agonist	Sulfite related allergic reactions, ventricular ectopy, ventricular arrhythmias
FDA Approved – other therapies					
Vasostrict (vasopressin)	Hypotension and shock	2014	Intravenous infusion: Post-cardiotomy shock: 0.03 to 0.1 units/minute Septic shock: 0.01 to 0.07 units/minute	Vasopressin receptor (V1, V2, V3) agonist	Decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital)
Angiotensin II	Hypotension and shock	2017	Intravenous infusion: 20 to 80 nanograms (ng)/kg/min	Angiotensin II receptor type 1 agonist	Venous and arterial thrombotic and thromboembolic events

Product (s) Name	Relevant Indication	Approval	Dose and Route of Administration	Mechanism of action	Key Warnings and Precautions
Non-FDA approved therapies					
Epinephrine	Approved for anaphylaxis and intraocular surgery; Used off-label for shock	1939	Off-label use Intravenous infusion: 0.05-2 mcg/kg/min	Non-selective alpha- and beta-adrenergic agonist	Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina

2. Regulatory Background

U.S. Regulatory Actions and Marketing History

Pitressin (vasopressin injection) is a pre-1938 drug product that has been commercially available for over 100 years. Vasopressin injection is an unapproved product that has been marketed in the United States by AR (formerly Luitpold Inc.) from September 1993 through November 1, 2012 for the prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in treatment of DI. It has also been used off-label for the treatment of esophageal varices, gastrointestinal hemorrhage, cardiac arrest, septic shock, and vasodilatory shock.

In June 2006, the FDA announced a new drug safety initiative to remove unapproved drugs from the market. In response to this initiative, NDA 204485 for vasopressin injection was submitted, which was approved on April 17, 2014. The FDA approved vasopressin is Vasostrict (NDA 204485), manufactured by Par Pharmaceutical Companies, Inc., Spring Valley, New York, and indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. The approved dose for Vasostrict is 0.03 to 0.1 units/minute to treat post-cardiotomy shock, and 0.01 to 0.07 units/minute to treat septic shock. Vasostrict is the RLD for NDA 212593.

Summary of Presubmission/Submission Regulatory Activity

On June 26, 2013, at a pre-NDA meeting (PIND 118380) between FDA and the applicant (Luitpold Pharmaceuticals, now AR), FDA indicated that published literature can be used to support efficacy and safety of vasopressin in treatment of patients with vasodilatory shock.

On March 4, 2014, Luitpold submitted NDA 206643 for (b) (4) (Vasopressin Injection, USP), 20 units/mL. On May 2, 2014, FDA issued a Refusal to File Letter for NDA 206643 due to product quality issues. Specifically, the NDA lacked sufficient product stability data to grant the expiration for drug product (b) (4)

On November 8, 2018, at a Pre-NDA teleconference between Luitpold Pharmaceuticals and the FDA, CMC issues such as change in drug substance manufacturing, bioassay for product characterization, stability data, specifications for impurities, formulation composition, aggregation studies, and biowaiver request were discussed.

On March 29, 2019, AR, Inc. submitted a 505(b)(2) NDA for Vasopressin injection which is the subject of this review.

Foreign Regulatory Actions and Marketing History

No reported foreign regulatory action.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Office of Scientific Investigations (OSI)

Not applicable.

Product Quality

None identified.

Clinical Microbiology

None identified.

Nonclinical Pharmacology/Toxicology

None identified.

Clinical Pharmacology

None identified.

Devices and Companion Diagnostic Issues

Not applicable.

Consumer Study Reviews

Not applicable.

4. Sources of Clinical Data and Review Strategy

Table of Clinical Studies

The applicant has submitted a systematic literature review of 35 studies published between April 14, 2014 (date of Vasostrict approval) and September 17, 2018, to identify any new data that may be inconsistent with FDA's previous findings of safety and efficacy for Vasostrict. Of these 35 studies, 11 trials were provided to support efficacy and safety, 5 studies were provided to support safety, 4 were systematic literature reviews, and 15 were case reports.

Of the 11 trials, 5 were prospective placebo- or active-controlled studies - Gordon 2014[10], Gordon 2016[11], Barzegar 2016[12], Barzegar 2017[13], and Hammond 2018[14]. Barzegar 2016, Barzegar 2017, and Hammond 2018 compared the use of fixed dose AVP and NE to NE alone. Gordon 2014 and Gordon 2016 evaluated the use of hydrocortisone (HCT) versus placebo on background therapy with AVP or NE. None of these controlled trials evaluated change in MAP as a primary endpoint; only 4 trials reported MAP at baseline and after treatment initiation (Barzegar 2016, Barzegar 2017, Gordon 2014, Gordon 2016) ; and only 2 trials evaluated the use of AVP on background therapy with a catecholamine (Barzegar 2016, Barzegar 2017). Table 2 lists the 4 randomized, controlled clinical trials that evaluated the use of AVP and also provided data on changes in MAP after initiation of AVP. The risk of bias in these trials was assessed as high by the applicant, based on the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[10]

[10] Higgins J, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(d5928).

Table 2. List of Clinical Trials Relevant to this NDA (Source: Reviewer compilation)

Trial Identity	Study Location/ Number of centers	Trial Design	Dose Regimen	Study Primary Endpoints	Duration of Follow up	Study Population / Total Number of Subjects (N)
Gordon 2014[11]	United Kingdom / 3	Prospective, randomized, open-label	AVP* 0.06 U/min titrated to MAP 65 – 75 mm Hg followed by HCT+ versus placebo administration	Plasma AVP concentration	2-25 days	Patients ≥ 16 years, with sepsis requiring vasopressors despite fluid resuscitation N = 61
Gordon 2016[12]	United Kingdom/ 18	Randomized, double-blinded, controlled, 2x2 factorial	AVP: up to 0.06 U/min or NE* up to 12 mcg/min titrated to MAP* 65 – 75 mm Hg followed by HCT versus placebo administration	Kidney failure-free patients at 28 days and kidney failure-free days in patients who developed kidney failure	28 days	Patients ≥ 16 years, with sepsis requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after onset of shock N = 421
Barzegar 2016[13]	Iran/ 1	Prospective, randomized, open-label	NE titrated to MAP ≥ 65 mm Hg +/- AVP 0.03 U/min	Venous lactate levels and lactate clearance	28 days	Patients ≥ 18 years, with septic shock, < 12 hours since ICU admission N = 45
Barzegar 2017[14]	Iran/ 3	Randomized, open-label, parallel	NE titrated to MAP ≥ 65 mm Hg +/- AVP 0.03 U/min	Sepsis biomarkers	28 days	Patients ≥ 18 years, with septic shock, < 12 hours since ICU admission N = 45

*AVP: Arginine Vasopressin, NE: Norepinephrine, MAP: mean arterial pressure, HCT: hydrocortisone phosphate

+HCT dose used: 50 mg every 6 hours or five days, then every 12 hours for three days, and once daily for three days

Review Strategy

Prospective, randomized, controlled trials are the gold standard to evaluate efficacy of an intervention. An increase in MAP is considered an acceptable measure of efficacy of

[11] Gordon AC, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med. 2014b;42(6):1325-33. PMID: 24557425

[12] Gordon AC, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18. PMID: 27483065

[13] Barzegar E, et al. The Therapeutic Role of Vasopressin on Improving Lactate Clearance During and After Vasogenic Shock: Microcirculation, Is It The Black Box? Acta Med Iran. 2016;54(1):15-23.PMID: 26853286

[14] Barzegar E, et al. Vasopressin in septic shock; assessment of sepsis biomarkers: A randomized, controlled trial. Indian Journal of Critical Care Medicine. 2017;21(9):578-84. PMID: 28970657

vasopressors. Hence, to support efficacy, 2 prospective, randomized trials that evaluated the use of AVP on background therapy with NE and provided data on change in MAP (Barzegar 2016, Barzegar 2017) were reviewed in detail. The review briefly summarizes other clinical studies submitted to support the efficacy of Vasopressin Injection.

5. Review of Relevant Individual Trials Used to Support Efficacy

Barzegar 2016

Trial Design Overview and Objectives

Barzegar 2016 is a prospective, randomized, controlled, open-label trial that evaluated the effect of early initiation of low-dose AVP (0.03 U/min) on the level and clearance of lactate as a marker of tissue perfusion in septic shock. Eligible patients were randomized to receive NE infusion titrated to achieve MAP ≥ 65 mm Hg or NE titrated to achieve MAP ≥ 65 mm Hg plus AVP infusion at a constant rate of 0.03 units/min (Exir Pharmaceutical Co. Tehran, Iran). Additional use of vasopressors (dopamine or epinephrine), inotropic agents (dobutamine), and HCT was at the discretion of the treating physician. No between group cross overs were permitted.

The trial was conducted between November 2012 and April 2014, in a 20-bed general surgical and emergency intensive care unit (ICU) of a tertiary teaching hospital (Sina hospital) in Tehran, Iran. The trial was approved by the Medical Ethics Committee of Tehran University of Medical Sciences (TUMS) (91-02-33-18310-63707) and a written informed consent was obtained from patients' next of kin.

Trial Endpoints

Primary endpoint: To compare venous lactate levels and lactate clearance at 24- and 48-hours between the two treatment arms.

Secondary endpoints: To compare hemodynamic parameters, arterial pH, NE requirements, mortality rate (ICU and 28-day mortality), and sepsis-related organ failure (SOFA) score between the two treatment arms.

Inclusion / Exclusion Criteria

Inclusion Criteria

The following patients were included in the trial:

- age > 18 years
- within 12 hours of diagnosis of septic shock as defined by the American college of chest physicians/society of critical care medicine consensus conference committee (two or more of Systemic Inflammatory Response Syndrome (SIRS)

criteria, infection [proven or suspected], new organ failure and hypotension)

Exclusion Criteria

- more than 12 hours of septic shock diagnosis
- previous AVP use
- mesenteric ischemia
- acute coronary syndrome
- heart failure (New York Heart Association class III or IV)
- hyponatremia (Na < 130 mmol/L)
- pregnancy
- patient with poor prognosis (death anticipated within hours), end-stage renal failure, vasospastic diseases
- recruitment in another clinical trial
- unwillingness to give written informed consent

Study Drug Discontinuation / Stopping Rules

Vasopressors were tapered off if the target MAP was maintained for more than 8 hours. AVP infusion was discontinued for shock resolution, or occurrence of life-threatening adverse events (digital ischemia, mesenteric ischemia, arrhythmias, serum sodium less than 130 mEq/ml), or patient death.

Study Schedule of Assessments

The following parameters were recorded / monitored during the trial:

- Baseline subject demographics and co-morbidities
- Baseline Simplified Acute Physiologic Score (SAPS) II for assessment of severity of illness
- Baseline and daily record of SOFA score as marker of organ dysfunction
- Continuous monitoring (per ICU protocol) of hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, central venous pressure (CVP), body temperature and oxygen saturation
- Baseline, 24- and 48-hours after randomization, serum levels of lactate, sodium, white blood cell count (WBC), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and creatinine; and arterial blood gas
- Baseline level of procalcitonin
- Baseline and daily electrocardiogram
- As clinically indicated, cardiac enzymes, echocardiogram, and other diagnostic imaging
- During ICU admission and 28 days after randomization, survival status

- Daily monitoring of adverse events
- Daily NE requirement

Statistical Analysis

The study had an 80% power to detect a 1.6 mmol/L difference in lactate levels at 24 and 48 hours at a significance level of 0.05. A standard deviation of 1.6 mmol/l in lactate level was assumed.

Patient disposition

A total of 30 patients who met the eligibility criteria were randomly assigned to NE or NE+AVP arm and completed the trial.

Results

There were no significant differences in the baseline demographic and clinical characteristics of subjects between the two treatment arms. There were no significant differences in the lactate level at 24- and 48-hours between the two arms - NE vs. AVP+NE (28.4 vs. 23.1 mg/dl, P=0.67 and 15.8 vs. 10.3 mg/dl, *P*=0.47, respectively). Lactate clearance at 24-hours was lower in NE compared to AVP+NE arm (21 vs. 46%, P=0.048), and at 48-hours was not different between the two arms.

Baseline hemodynamic parameters were comparable between the two treatment arms. The MAP at 24-hours was statistically significantly higher in the AVP+NE arm compared to NE arm, and at 48-hours, there was no difference between the two arms (table 3). According to the author, the NE dose requirements were lower in the NE+AVP arm, but no details were provided.

Table 3. Changes in hemodynamic parameters in Barzegar 2016 Trial[13] (Source: Published journal article)

	Baseline	*P*-value	24 hr	*P*.value	48 hr	*P*-value
HR beats/min						
NE	87.2±18	0.663	105.4±10.1	0.003	104.8±7.8	0.0001
AVP	90.2±19.2		86.9±18.9		85.1±11.1	
SBP, mm Hg						
NE	75.1±11.1	0.295	101.8±27.6	0.032	123.5±19.4	0.790
AVP	80.±14		121.9±20.3		121.5±15.6	
MAP, mm Hg						
NE	62.2±6.5	0.613	79.5±10.4	0.044	82.1±16.3	0.671
AVP	65.4±6.4		87.6±10.4		85.1±16	
CVP mm Hg H2O						
NE	11.5±11.2	0.41	17.3±6.2	0.86	11.1±9.8	0.16
AVP	15.4±4.9		16.9±5.3		16.9±4.9	

HR: heart rate, NE: norepinephrine, AVP: arginine vasopressin, SBP: systolic blood pressure, MAP: mean arterial pressure, CVP: central venous pressure

Reviewer Comments*: Data from Barzegar 2016 trial suggest that AVP increases MAP when used in addition to NE in patients with septic shock. As this trial was not powered to evaluate a change in MAP as a primary endpoint, these results are only considered as supportive evidence of vasopressor effect of AVP.*

Barzegar 2017

Trial Design Overview and Objectives

Barzegar 2017[14] is a prospective, randomized, controlled, open-label trial that evaluated the effect of early initiation of low-dose AVP (0.03 U/min) on biomarkers of sepsis in patients with septic shock. The biomarkers evaluated in this study included interleukin-6 (IL-6), interleukin-10 (IL-10), pentraxin 3 (PTX3), angiopoietin 1 (Ang-1), and angiopoietin 2 (Ang-2). Generally, the trial design (except the endpoints), eligibility criteria, study drug discontinuation/ stopping rules, schedule of study assessments, and time period of the trial were similar to Barzegar 2016. Additional information is provided under relevant subsections.

Trial Endpoints

Primary endpoint: To compare the levels of biomarkers for sepsis between the two treatment arms.

Secondary endpoints: To compare hemodynamic parameters, NE requirements, mortality rate (ICU and 28-day mortality), organ failure, and effect of corticosteroids on the biomarkers between the two treatment arms.

Study Schedule of assessments

In addition to the study assessments mentioned under Barzegar 2016, blood samples to measure biomarkers for sepsis (IL-6, IL-10, PTX3, Ang-1, and Ang-2) were collected at baseline, 24 hrs, and 48 hrs after randomization.

Statistical Analysis

Sample size calculation is not described in the publication.

Patient disposition

A total of 45 patients who met the eligibility criteria were randomly assigned to NE or NE+AVP arm, and 42 subjects completed the trial.

Results

There were no significant differences in the baseline demographic and clinical characteristics of subjects between the two treatment arms. There were no significant differences in the levels of biomarkers for sepsis at 24- and 48-hours between the two arms - NE vs. AVP+NE.

Baseline hemodynamic parameters were comparable between the two treatment arms. The MAP at 24-hours was statistically significantly higher in the AVP+NE arm compared to NE arm, and at 48-hours, there was no difference between the two arms (table 4). At 24- and 48-hours, the heart rate and dose requirements for NE were lower in the NE+AVP arm (table 4).

Table 4. Changes in Hemodynamic Parameters and NE Infusion rate in Trial Barzegar 2017[14] (Source: Published journal article)

	Baseline	*P*	24 h	*P*	48 h	*P*
HR (beats/min)						
NE	87.1±18.5	0.76	105±10.2	0.001	106.8±8.1	0.001
AVP	89.8±18		85.4±16.2		87.2±10.1	
SBP (mmHg)						
NE	75.7±11.1	0.73	98.2±31.3	0.002	120.1±18.8	0.40
AVP	77±12.8		124.4±18.6		125.5±18.5	
MAP (mmHg)						
NE	62.1±6.2	0.32	77.8±12.7	0.008	74±22	0.10
AVP	64.1±6.4		87.3±9		84.4±14.6	
CVP (mmHg H_2O)						
NE	10.1±11.2	0.67	16.3±5.4	0.90	12.3±8.5	0.10
AVP	11.7±8.1		16.5±4.9		16.7±5	
Creatinine (mg/dl)						
NE	1.4±0.5	0.42	1.6±0.4	0.22	1.7±0.9	0.29
AVP	1.3±0.6		1.4±0.6		1.4±0.7	
NE infusion rate (µg/min)						
NE	12.7±4.2	0.62	13.5±5.6	0.001	8.3±4.5	0.013
AVP	13.3±4.3		5.2±4		4.5±3.8	

***Reviewer Comments**: Similar to Barzegar 2016, data from Barzegar 2017 trial suggest that AVP increases MAP when used in addition to NE in patients with septic shock. As this trial was not powered to evaluate a change in MAP as a primary endpoint, these results are only considered as supportive evidence of vasopressor effect of AVP.*

Other Studies to Support Efficacy

Gordon 2014[11] and **Gordon 2016[12]** utilized AVP as background therapy to evaluate the effects of HCT versus placebo on level of AVP and renal outcomes, respectively. Hence, these studies are not informative on the effect of AVP on MAP on background therapy with catecholamines.

Hammond 2018[15] was a single-center, open-label trial that compared the time to achieve and maintain a target MAP of 65 mm Hg between NE + AVP, versus NE alone. Hammond 2018 demonstrated that use of NE+AVP significantly decreased the time to achieve and maintain the

[15]Hammond DA, et al. Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock. Pharmacotherapy. 2018;38(5):531-8. PMID: 29600824

target MAP (5.7 hours (interquartile range [IQR] 1.7–10.3 hrs), compared with 7.6 hours (IQR 3.6–16.7 hrs, p=0.058). However, data on changes in MAP was not provided.

Buckley 2017[16] was a retrospective cohort study evaluating the catecholamine-sparing effect of AVP at 0.04 units/min and/or HCT in patients with septic shock and demonstrated that concomitant AVP and HCT was associated with additive catecholamine-sparing effect compared to either agent alone.

Hajjar 2017[17] was a prospective, randomized, double-blind trial evaluating the effect of AVP versus NE administered to maintain MAP, on mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure) within 30 days in patients with vasoplegic shock after cardiac surgery. Hajjar 2017 enrolled 330 patients and demonstrated that the incidence of mortality or severe complications was lower in the AVP versus NE arm 32 %; 95% CI, 24.7 to 39.7 versus 49%; 95% CI, 41.0 to 57.0 (adjusted hazard ratio, 0.52; 95% CI, 0.36 to 0.75; *P* = 0.0005). With AVP, the median MAP increased from 55 (50-60) mm Hg at baseline to 73 (70-77) mm Hg at 12 hours post infusion. The increase in MAP was similar between the AVP and NE arms.

Nguyen 2017[18] and **Ohsugi 2019**[19] are retrospective studies that evaluated the effect of a second vasoactive agent in patients with septic shock receiving NE on mortality and demonstrated that AVP did not decrease mortality in patients with septic shock.

Published literature pertaining to any pediatric age group was not reviewed.

Reviewer Comments: *These studies have several study design limitations and confounding factors that limit the conclusions that can be drawn about the effect of AVP on MAP in patients with septic shock unresponsive to fluids and catecholamines.*

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[16] Buckley MS, et al. Concomitant vasopressin and hydrocortisone therapy on short-term hemodynamic effects and vasopressor requirements in refractory septic shock. Journal of Critical Care. 2017;42:6-11.

[17] Hajjar LA, et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. Anesthesiology. 2017;126(1):85-93. PMID: 27841822. https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/ALN/B/ALN_2016_10_07_HAJJAR_ALN-D-16-00041_SDC1.pdf

[18] Nguyen HB, et al. Comparative Effectiveness of Second Vasoactive Agents in Septic Shock Refractory to Norepinephrine. J Intensive Care Med. 2017;32(7):451-9. PMID: 27189952

[19] Ohsugi K, et al. Does vasopressin improve the mortality of septic shock patients treated with high-dose NA. Indian J Crit Care Med. 2016;20(3):137-40. PMID: 27076723

6. Review of Safety

Safety Review Approach

To support safety of AVP, 8 published studies, 15 case reports, and adverse event reports from the applicant's post-marketing surveillance database and the FDA adverse event reporting system, were reviewed. No patient-level data were provided. The sources of safety data did not distinguish between serious adverse events (SAEs) or adverse events (AEs).

Review of the Safety Database

Overall Exposure

Overall, 2,255 adult subjects were exposed to 0.01 to 0.08 U/min of IV AVP infusion titrated to a MAP ≥ 65 mm Hg for a duration ranging between ≤ 24 hours to > 48 hours in 14 clinical studies reported in the literature. A precise average duration of AVP infusion could not be determined from the published literature.

Safety Results

Controlled Clinical Trials

Table 5 displays the AEs reported by five controlled clinical trials of AVP, 5 in adult subjects (Gordon 2014, Gordon 2016, Barzegar 2016, Hajjar 2017), and 1 in pediatric subjects (Rios 2015). The overall incidence of reported AEs in these trials was 17.5% in the AVP arm versus 15.0% in the comparator arm (dopamine or NE or NE/HCT). The most common AEs with an incidence of > 1% and reported at a higher rate in the AVP arm, were hyponatremia (3.7%), digital ischemia (3.2%), mesenteric ischemia (1.7%), and acute coronary syndrome (1.5%).

Gordon 2014 compared AVP+HCT versus AVP+placebo and reported a total of 14 AEs, included in the summary table 5. These AEs were extension of a pre-existing recent ischemic cerebral infarct (n=1), cool/mottled peripheries (n=4), rise in serum lactate (n=1), and rise in troponin (n=1).

Reviewer Comments*: In Gordon 2014 trial, all subjects received AVP. As there was no comparator to AVP and the AEs were not reported by study arm, counting these events in summary table 5, bias the finding of AEs toward the AVP arm.*

Barzegar 2017 reported that rate of AEs (arrhythmia, digital ischemia,

and hyponatremia) was similar in both groups but these rates were not reported

and not counted in summary table 5.

Hajjar 2017 was a controlled trial of subjects with vasoplegic shock after cardiac surgery and found a lower occurrence of atrial fibrillation (AF) in the AVP versus NE group (63.8% vs. 82.1%; P < 0.001). There was no difference in the rates of digital ischemia, mesenteric ischemia, hyponatremia, or myocardial infarction between the two groups.

There was no difference in in-hospital, 28-day, or 30-day mortality rates between AVP and comparator groups in trials - Gordon 2014, Gordon 2016, Barzegar 2016, Barzegar 2018, Hammond 2018, and Hajjar 2017.

Rios 2015 enrolled 20 hypotensive infants who received AVP (n=10) or dopamine (n=10) and reported 4/10 deaths in the AVP arm and 2/10 deaths in the comparator arm . No other AEs were reported in the Rios 2015 publication.

Table 5. Adverse events reported in controlled clinical trials of Vasopressin by study arms (Source: Applicant table 4, page 11 of the summary of clinical safety)

	Vasopressin (rate ranges)			Comparators			
Body System/Adverse Event	**< 0.04 (U/min) (Rios, 2015; Barzegar, 2016; Barzegar 2017) n = 48 (13%)**	**> 0.04 (U/min) (Gordon, 2016; Gordon, 2014; Hajjar, 2017) n = 415 (90%)**	**Total (%) n = 463**	**Dopamine 5 mcg/kg/min (Rios 2015) n = 10 (2.3%)**	**NE 5-60 µg/min (Barzegar 2016; Gordon, 2016, Hajjar, 2017, Barzegar 2017) n = 307 (73.3%)**	**NE/HCT 12 µg/min/ 200 mg/day (Gordon 2016) n = 102 (24.4%)**	**Total (%) n = 419**
Acute coronary syndrome	0	7 (1.7%)	7 (1.5%)	0	0	2 (2.0%)	2 (0.4%)
Arrhythmia	1 (2%)	0	1(0.2%)	0	3 (1.0%)	0	3 (0.6%)
Cardiac arrest	1 (2%)	0	1 (0.2%)		3 (1.0%)	0	3 (0.6%)
Life-threatening arrhythmia	0	2 (0.5%)	2 (0.4%)	0	4 (1.3%)	1 (1.0%)	5 (1.2%)
Post-operative acute myocardial infarction	0	11 (2.7%)	11 (2.4%)	0	17 (5.5%)	0	17 (3.3%)
Hyponatremia	5 (10.4%)	12 (2.9%)	17 (3.7%)	3 (30%)	10 (3.3%)	0	13 (2.1%)
Hyperglycemia	3 (6.3%)	0	3 (0.6%)	2 (20%)	0	0	2 (0.4%)
Cool/mottled peripheries	0	3 (0.7%)	3 (0.6%)	0	0	0	0
Extension of a preexisting recent ischemic cerebral infarct	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Rise in serum lactate	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Rise in troponin	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Digital ischemia	1 (2%)	14 (3.4%)	15 (3.2%)	0	3 (1.0%)	2 (2.0%)	5 (0.4%)
Mesenteric ischemia	0	8 (1.9%)	8 (1.7%)	0	3 (1.0%)	4 (4.0%)	7 (1.3%)
Hypertension	2	0	2 (0.4%)	0	0	0	0
Other	0	4 (1.0%)	4 (0.9%)	0	1 (0.33%)	3 (3.0%)	4 (0.8%)
Death	4 (8.3%)	0	4 (0.9%)	2 (20%)	0	0	2 (0.4%)
Totals	17 (35.4%)	64 (15.4%)	81(17.5%)	7 (70%)	44 (14.3%)	12 (11.8%)	63 (15.0%)

Reviewer Comments: *The applicant summary table 5 is limited by 1) lack of comparator arm in Gordon 2014 trial, 2) incomplete reporting of AEs Barzegar 2017, 3) inclusion of a pediatric study (Rios 2015), and 4) varied study designs and comparators. The label of the RLD and the proposed label states that "the most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital)." The AEs reported in the published controlled clinical trials submitted by the applicant are consistent with FDA's previous findings of safety with the RLD. Hence, no labeling change is indicated for section 6 Adverse Reactions.*

Observational Studies

Table 6 displays the AEs with AVP reported in three observational studies (Reardon 2014, Anantasit 2014, and Bissell 2015). The overall incidence of reported AEs was 19% in the AVP arm versus 11.9% in the comparator arm (NE or HCT). The most common AEs with an incidence of > 1% and reported at a higher rate in the AVP arm were AF (4.3%), ventricular tachycardia (2.5%), myocardial ischemia (2.5%), mesenteric ischemia (1.6%), and arrhythmia (1.6%). The label for Vasostrict describes AF, and tachyarrhythmias as adverse reactions.

Table 6. Adverse events reported in observational studies of Vasopressin by study arms (Source: Applicant table 5, page 14 of the summary of clinical safety)

	Vasopressin	Comparators		
Body System/Adverse Event	Ranges 0.01-0.04 (U/min) (Reardon, 2014; Anantasit, 2014; Bissell 2015) n = 516	NE 5-15 µg/min (Anantasit, 2014) n = 715	HCT 200 mg/day (Bissell, 2015) n = 31	Total (%) n = 746
Arrhythmia	8 (1.6%)	0	5 (16%)	5 (0.67%)
Cardiac arrest	2 (0.39%)	0	0	0
Atrial fibrillation	22 (4.3%)	0	0	0
Bradyarrhythmia	6 (1.2%)	11 (1.5%)	0	11 (1.5%)
Tachyarrhythmia	5 (0.97%)	15 (2.1%)	0	15 (2.0%)
Ventricular fibrillation	1 (0.2%)	0	0	0
Ventricular tachycardia	13 (2.5%)	0	0	0
Hyponatremia	3 (0.6%)	1 (0.14%)	4 (13%)	5 (0.67%)
Hyperglycemia	6 (1.2%)	0	9 (29%)	9 (1.2%)
Superinfection	1 (0.2%)	0	10 (32%)	10 (1.3%)
Digital ischemia	4 (0.8%)	4 (0.6%)	0	4 (0.54%)
Mesenteric ischemia	8 (1.6%)	8 (1.1%)	0	8 (0.11%)
Myocardial ischemia	13 (2.5%)	13 (1.8%)	0	13 (1.7%)
Cerebrovascular accident	2 (0.39%)	7 (1%)	0	7 (0.93%)
Other	4 (0.8%)	2 (0.3%)	0	2 (0.27%)
Totals	98 (19%)	61 (8.5%)	28 (90%)	89 (11.9%)

Post market surveillance data

The applicant's post market surveillance adverse event data by the highest level MedDRA system organ class (SOC) categories based on its pharmacovigilance data retrieved 40 AEs, with the most common AEs (in decreasing order) being metabolic and nutrition disorders (25 %), endocrine disorders (15%), vascular disorders (12.5%), cardiac disorders (10%), general disorders and administration site conditions (7.5%), and nervous system disorders (7.5%).

The applicant's post market surveillance adverse event data by highest level MedDRA system organ class (SOC) categories based on FDA Adverse Event Reporting System (FAERs) database retrieved 740 AEs with the most common AEs (in decreasing order) being general disorders and administration site conditions (n=176, 23.78%), product issues (n=137, 18.51%), cardiac disorders (n=122, 16.49%), renal and urinary disorders (n = 42, 5.7%), and nervous system disorders (n = 40, 5.4%).

The sponsor did not provide additional details about AEs related to product issues. An internal search of the FAERS database by OSE retrieved 67 serious reports coded with the MedDRA term "Drug ineffective" between 2013 and 2019. A review of 8 random sample case reports by OSE showed that these patients had severe conditions such as medication-overdose-induced severe metabolic acidosis, post-surgical sepsis, post-surgical cardiac arrest, vasoplegia refractory to vasopressors, flecainide toxicity, and Haemophagocytic lymphohistiocytosis mimicking sepsis. Most of these reports mention that the patient was refractory to norepinephrine and other vasopressors including vasopressin. Vasopressin has not been marketed since November 1, 2012. From the available information, it is difficult to determine if there is truly a product quality issue or a non-response to treatment due to the severity of the underlying illness.

Special Populations

Pediatrics: The efficacy and safety of AVP in vasodilatory shock in pediatric patients has not been established. The applicant identified two pediatric studies (Rios 2015, Iliopoulos 2017) during the systematic review. Other than mortality, these studies did not report safety outcomes.

Geriatric Use: The clinical studies of AVP do not provide safety data based on age groups.

The applicant did not provide any additional data to inform use of AVP in pregnancy and lactation, renal or hepatic impairment, or the drug abuse potential of AVP.

Withdrawal and Rebound

Applicant's systematic literature search revealed 10 case reports of transient diabetes insipidus (DI) after discontinuation of AVP infusion. DI was treated with re-initiation of AVP and/or Desmopressin, and fluid administration and most cases resolved within 24 -48 hours of onset of DI. In these case reports, the age range of

patients was 23 to 58 years old. indications for AVP use included septic shock, vasospasm, and acute and chronic neurological conditions; and duration of initial treatment with AVP ranged from 15 hours to 5 days.

Reviewer Comments: *The mechanism of DI after withdrawal of AVP is not well understood. Clinical presentation of transient DI after cessation of AVP infusion indicates that these may be cases of nephrogenic DI. A proposed mechanism for occurrence of nephrogenic DI is the downregulation of V2 receptors during treatment with AVP, described in literature as renal escape from antidiuresis[20].*

7. Consultations

On July 10, 2019, the Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pharmacovigilance I (DPV-I), Office of Surveillance Epidemiology (OSE) to conduct a FAERS search for post market adverse event cases with a serious outcome for adult and pediatric patients with Pitressin (vasopressin) injection from January 1, 2013 to present to help support the NDA review.

DPV-I searched the FAERS database for time period of January 1, 2013 – September 17, 2019. This search retrieved 270 and 60 reports for vasopressin with a serious outcome and death, respectively. In reports of serious outcome, that provided patient's age, there were 185 reports for adults and 35 reports for pediatric age group.

In adults with reports with a serious outcome, the most frequently reported MedDRA Preferred Term (PT) AEs were drug ineffective (n=67), hypotension (n=33), DI (n=19), and shock (n=16). The PTs not currently mentioned in the label for Vasostrict included optic atrophy (n=7), blindness (n=5), blindness, cortical (n=5), optic nerve injury (n=5), retinal ischemia (n=5), and visual impairment (n=5).

To identify the presence of a new safety signal, DPV-I data mining using the Empirica Signal software for vasopressin reports with a serious outcome received by FDA. The consult states that, "*DPV-I identified cases of transient diabetes insipidus occurring upon withdrawal of vasopressin as an unexpected adverse event and a potential safety signal for DCaRP's consideration for the purpose of review of NDA 212593 (vasopressin injection).*"

Reviewer Comments: *The finding of cases of transient DI by DPV-I FAERS data analysis is consistent with the case reports of DI submitted by the sponsor. Based on the review of case reports in literature and FAERS data analysis by DPV-I, transient DI after discontinuation of vasopressin is a new safety signal and should be considered for inclusion in the label.*

[20] *Michael A. Bohl, James Forseth, Peter Nakaji. Transient Diabetes Insipidus After Discontinuation of Vasopressin in Neurological Intensive Care Unit Patients: Case Series and Literature Review. World Neurosurg. (2017) 97:479-488.*

8. Labeling Recommendations

The potential for the development of transient DI after cessation of AVP infusion should be included in the label for Vasopressin Injection, USP and the label for Vasostrict should be accordingly revised.

Addendum dated July 7, 2020: As this NDA relied on data from published literature, financial certification and disclosure documents are not applicable.

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

/s/

CHARU GANDOTRA
07/07/2020 01:54:20 PM

CLINICAL REVIEW

Application Type	505(b)(2) NDA
Application Number(s)	212593
Priority or Standard	Standard
Submit Date(s)	March 29, 2019
Received Date(s)	March 29, 2019
PDUFA Goal Date	January 29, 2020
Division/Office	Division of Cardiovascular and Renal Products / OND
Reviewer Name(s)	Charu Gandotra MD
Review Completion Date	November 29, 2019
Established/Proper Name	Vasopressin
(Proposed) Trade Name	Vasopressin Injection, USP
Applicant	American Regent, Inc.
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	Intravenous infusion titrated (b) (4) Post-cardiotomy shock: 0.03 to 0.1 units/minute Septic shock: 0.01 to 0.07 units/minute
Applicant Proposed Indication(s)/Population(s)	Increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines

Table of Contents

1. Executive Summary

On March 29, 2019, American Regent (AR), Inc. submitted a 505(b)(2) New Drug Application for Vasopressin Injection, USP, 20 units/mL single dose vial, to be administered as an infusion for treatment of patients with vasodilatory shock who remain hypotensive despite fluids and catecholamines. AR proposed to rely on FDA's findings of safety and efficacy for Vasostrict, the Reference Listed Drug (RLD) for Vasopressin. Vasostrict (vasopressin) (NDA 204485) manufactured by Par Pharmaceutical Companies, Inc., Spring Valley, New York was approved by FDA on April 17, 2014, to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. Approved dose for Vasostrict is 0.03 to 0.1 units/minute to treat post-cardiotomy shock, and 0.01 to 0.07 units/minute to treat septic shock.

NDA 212593 is based on literature published between April 14, 2014 (date of Vasostrict approval) and September 17, 2018, to identify any new data that may be inconsistent with FDA's previous findings of safety and efficacy for Vasostrict. The applicant submitted 35 studies - 11 trials to support efficacy and safety, 5 studies to support safety, 4 systematic literature reviews, and 15 case reports.

For efficacy, the clinical review focused on 2 prospective, randomized trials that evaluated the use of vasopressin (AVP) on background therapy with norepinephrine (NE) and provided data on change in mean arterial pressure (MAP). For safety, the clinical review focused on published literature, and information from the applicant's pharmacovigilance database and the FDA adverse event reporting system. In summary, the published literature continues to support FDA's previous findings of safety and efficacy for AVP. A new safety signal of development of transient diabetes insipidus (DI) after discontinuation of AVP infusion was identified based on case reports. Most cases of DI resolved within 24 hours with treatment comprised of intravenous fluids, re-initiation of AVP infusion, and/or Desmopressin. This finding does not change the overall benefit-risk profile for AVP.

In conclusion, from a clinical perspective, the application may be approved. The potential for the development of transient DI after cessation of AVP infusion should be included in the label for Vasopressin Injection, USP and the label for Vasostrict should be accordingly revised.

1. Therapeutic Context

Analysis of Condition

Vasodilatory shock (VS) is characterized by hypotension due to decreased systemic vascular resistance, tissue hypoperfusion leading to inadequate cellular oxygen utilization, increase in levels of lactate, and organ failure. VS comprises of ≥ 66% of all types of shock.[1] Septic shock is the most common etiology of VS. The true incidence of sepsis and septic shock is not known. The frequency of septic shock in patients admitted to intensive care unit (ICU) is estimated at 10.4%[2]. Other causes of VS include anaphylaxis, neurogenic shock, cardiovascular surgery requiring cardiopulmonary bypass, etc.[3] Shock is associated with a high mortality rate of 30 to 50%.[2]

Analysis of Current Treatment Options

The recommended treatment for VS includes intravenous (IV) administration of fluids and vasopressors to achieve a target MAP of ≥ 65 mm Hg.[3] Adjunctive therapy with IV inotropic agents and hydrocortisone (HCT)[4] may be needed in refractory cases of VS. NE is the first-line vasopressor indicated to treat VS. AVP or epinephrine or angiotensin II can be added to NE to increase MAP, or AVP can be added to reduce the dose of NE. In advanced stages of VS, adrenergic hyposensitivity leading to a loss of catecholamine pressor effect has been observed.[5]

In rare circumstances, dopamine can be used as an alternative to NE, for example in patients with low risk for tachyarrhythmias. Dobutamine may be used in patients who have persistent hypoperfusion despite adequate fluid resuscitation and use of vasopressors[6].

Approved therapies to treat patients with hypotension in shock have not

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[1] Abril MK, Khanna AK, Kroll S, McNamara C, Handisides D, Busse LW. Regional differences in the treatment of refractory vasodilatory shock using Angiotensin II in High Output Shock (ATHOS-3) data. J Crit Care. 2018;50:188–94.

[2] Jean-Louis Vincent, Gabriel Jones, Sholto David, Elena Olariu & Kevin K. Cadwell. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Critical Care volume 23, Article number: 196 (2019).

[3] Prielipp R, et al. Cardiovascular failure and pharmacologic support after cardiac surgery. New Horizons: An official publication of theSociety of Critical Care Medicine. 1999;7(4):16. PMID: NA

[4] J.C. Jentzer, S. Vallabhajosyula, A.K. Khanna, L.S. Chawla, L.W. Busse, K.B. KashaniManagement of refractory vasodilatory shock Chest, 154 (2) (2018), pp. 416-426

[5] Dunser MW, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation. 2003a;107(18):2313-9. PMID: 12732600

[6] Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

demonstrated an effect on clinical outcomes or mortality. A demonstration of efficacy to increase MAP in patients with shock has been the regulatory basis for approval, as maintenance of blood pressure is important to preserve vital organ function and allows time for disease specific intervention(s). In 2017, FDA approved angiotensin II acetate (Giapreza 2.5 mg/ml Injection, NDA 209360) to increase blood pressure in adults with septic or other distributive shock based on the demonstration of efficacy of angiotensin in raising MAP. Table 1 summarizes the currently available therapies to increase MAP.

AVP is approved as Vasostrict to treat patients with VS. AVP, also known as the antidiuretic hormone, regulates plasma osmolality and extracellular fluid volume at physiologic levels. Increase in plasma osmolality and decrease in blood pressure stimulate the release of AVP. AVP exerts it's vasopressor effect through AVP type 1 (V1) receptors in the vasculature and it's antidiuretic effect through AVP type 2 (V_2) receptors in the kidney. AVP acts as a vasoconstrictor without much antidiuretic effect only during periods of hypovolemia and hypotension.[7] In the intestinal tract, AVP increases peristaltic activity, especially of the large bowel. Hence, AVP is used to treat hypotension associated with shock and its synthetic analogue, Desmopressin is used to treat diabetes insipidus (DI). Off-label uses of AVP include treatment of cardiac arrest, prevention or relief of intestinal paresis, dispel interfering gas shadows and/or to concentrate contrast media prior to abdominal radiographic procedures.[8,9]

[7] Gordon AC, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients with Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18. PMID: 27483065

[8] Dunser MW, et al. A century of arginine vasopressin research leading to new therapeutic strategies. Anesthesiology. 2006;105(3):444-5. PMID: 16931974

[9] Treschan TA, et al. The vasopressin system: physiology and clinical strategies. Anesthesiology. 2006;105(3):599-612; quiz 39-40. PMID: 16931995

Table 1. Currently Available Treatment for the Proposed Indication of Vasodilatory Shock

Product (s) Name	Relevant Indication	Approval	Dose and Route of Administration	Mechanism of action	Key Warnings and Precautions
FDA Approved - Catecholamines					
Nor-epinephrine	Hypotension	2007	Intravenous infusion: 8 to 12 mcg/min	Beta-1 and Alpha-1 adrenergic receptor agonist	Bradycardia
Phenylephrine	Hypotension	1954	Bolus intravenous injection: 40 mcg to 200 mcg Intravenous infusion: 10 mcg/min to 35 mcg/min, titrating to effect, not to exceed 200 mcg/min	Alpha-1 adrenergic receptor agonist	Exacerbation of angina, heart failure, or pulmonary arterial hypertension Excessive peripheral and visceral vasoconstriction Severe bradycardia and decreased cardiac output Increase the need for renal replacement therapy in patients with septic shock
Dopamine	To correct hemodynamic imbalances	1983	Intravenous infusion: 2 to 50 mcg/kg/min	Dopamine, Beta-1 and Alpha-1 adrenergic receptor agonist	Ventricular arrhythmias Excessive peripheral and visceral vasoconstriction
Ephedrine	Hypotension	2016	Intravenous bolus: 5 to 10 mg as needed, not to exceed 50 mg	Alpha- and beta-adrenergic agonist	Tachyphylaxis and tolerance
Metaraminol	Hypotension	1999	Intramuscular or subcutaneous injection: 2 to 10 mg Intravenous infusion: 15 to 100 mg	Alpha-1 adrenergic receptor agonist	Sulfite related allergic reactions, ventricular ectopy, ventricular arrhythmias
FDA Approved – other therapies					
Vasostrict (vasopressin)	Hypotension and shock	2014	Intravenous infusion: Post-cardiotomy shock: 0.03 to 0.1 units/minute Septic shock: 0.01 to 0.07 units/minute	Vasopressin receptor (V1, V2, V3) agonist	Decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital)
Angiotensin II	Hypotension and shock	2017	Intravenous infusion: 20 to 80 nanograms (ng)/kg/min	Angiotensin II receptor type 1 agonist	Venous and arterial thrombotic and thromboembolic events

Product (s) Name	Relevant Indication	Approval	Dose and Route of Administration	Mechanism of action	Key Warnings and Precautions
Non-FDA approved therapies					
Epinephrine	Approved for anaphylaxis and intraocular surgery; Used off-label for shock	1939	Off-label use Intravenous infusion: 0.05-2 mcg/kg/min	Non-selective alpha- and beta-adrenergic agonist	Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina

2. Regulatory Background

U.S. Regulatory Actions and Marketing History

Pitressin (vasopressin injection) is a pre-1938 drug product that has been commercially available for over 100 years. Vasopressin injection is an unapproved product that has been marketed in the United States by AR (formerly Luitpold Inc.) from September 1993 through November 1, 2012 for the prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in treatment of DI. It has also been used off-label for the treatment of esophageal varices, gastrointestinal hemorrhage, cardiac arrest, septic shock, and vasodilatory shock.

In June 2006, the FDA announced a new drug safety initiative to remove unapproved drugs from the market. In response to this initiative, NDA 204485 for vasopressin injection was submitted, which was approved on April 17, 2014. The FDA approved vasopressin is Vasostrict (NDA 204485), manufactured by Par Pharmaceutical Companies, Inc., Spring Valley, New York, and indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. The approved dose for Vasostrict is 0.03 to 0.1 units/minute to treat post-cardiotomy shock, and 0.01 to 0.07 units/minute to treat septic shock. Vasostrict is the RLD for NDA 212593.

Summary of Presubmission/Submission Regulatory Activity

On June 26, 2013, at a pre-NDA meeting (PIND 118380) between FDA and the applicant (Luitpold Pharmaceuticals, now AR), FDA indicated that published literature can be used to support efficacy and safety of vasopressin in treatment of patients with vasodilatory shock.

On March 4, 2014, Luitpold submitted NDA 206643 for (b) (4) (Vasopressin Injection, USP), 20 units/mL. On May 2, 2014, FDA issued a Refusal to File Letter for NDA 206643 due to product quality issues. Specifically, the NDA lacked sufficient product stability data to grant the expiration for drug product (b) (4)

On November 8, 2018, at a Pre-NDA teleconference between Luitpold Pharmaceuticals and the FDA, CMC issues such as change in drug substance manufacturing, bioassay for product characterization, stability data, specifications for impurities, formulation composition, aggregation studies, and biowaiver request were discussed.

On March 29, 2019, AR, Inc. submitted a 505(b)(2) NDA for Vasopressin injection which is the subject of this review.

Foreign Regulatory Actions and Marketing History

No reported foreign regulatory action.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Office of Scientific Investigations (OSI)

Not applicable.

Product Quality

None identified.

Clinical Microbiology

None identified.

Nonclinical Pharmacology/Toxicology

None identified.

Clinical Pharmacology

None identified.

Devices and Companion Diagnostic Issues

Not applicable.

Consumer Study Reviews

Not applicable.

4. Sources of Clinical Data and Review Strategy

Table of Clinical Studies

The applicant has submitted a systematic literature review of 35 studies published between April 14, 2014 (date of Vasostrict approval) and September 17, 2018, to identify any new data that may be inconsistent with FDA's previous findings of safety and efficacy for Vasostrict. Of these 35 studies, 11 trials were provided to support efficacy and safety, 5 studies were provided to support safety, 4 were systematic literature reviews, and 15 were case reports.

Of the 11 trials, 5 were prospective placebo- or active-controlled studies - Gordon 2014[10], Gordon 2016[11], Barzegar 2016[12], Barzegar 2017[13], and Hammond 2018[14]. Barzegar 2016, Barzegar 2017, and Hammond 2018 compared the use of fixed dose AVP and NE to NE alone. Gordon 2014 and Gordon 2016 evaluated the use of hydrocortisone (HCT) versus placebo on background therapy with AVP or NE. None of these controlled trials evaluated change in MAP as a primary endpoint; only 4 trials reported MAP at baseline and after treatment initiation (Barzegar 2016, Barzegar 2017, Gordon 2014, Gordon 2016) ; and only 2 trials evaluated the use of AVP on background therapy with a catecholamine (Barzegar 2016, Barzegar 2017). Table 2 lists the 4 randomized, controlled clinical trials that evaluated the use of AVP and also provided data on changes in MAP after initiation of AVP. The risk of bias in these trials was assessed as high by the applicant, based on the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[10]

[10] Higgins J, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(d5928).

Table 2. List of Clinical Trials Relevant to this NDA (Source: Reviewer compilation)

Trial Identity	Study Location/ Number of centers	Trial Design	Dose Regimen	Study Primary Endpoints	Duration of Follow up	Study Population / Total Number of Subjects (N)
Gordon 2014[11]	United Kingdom / 3	Prospective, randomized, open-label	AVP* 0.06 U/min titrated to MAP 65 – 75 mm Hg followed by HCT+ versus placebo administration	Plasma AVP concentration	2-25 days	Patients ≥ 16 years, with sepsis requiring vasopressors despite fluid resuscitation N = 61
Gordon 2016[12]	United Kingdom/ 18	Randomized, double-blinded, controlled, 2x2 factorial	AVP: up to 0.06 U/min or NE* up to 12 mcg/min titrated to MAP* 65 – 75 mm Hg followed by HCT versus placebo administration	Kidney failure-free patients at 28 days and kidney failure-free days in patients who developed kidney failure	28 days	Patients ≥ 16 years, with sepsis requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after onset of shock N = 421
Barzegar 2016[13]	Iran/ 1	Prospective, randomized, open-label	NE titrated to MAP ≥ 65 mm Hg +/- AVP 0.03 U/min	Venous lactate levels and lactate clearance	28 days	Patients ≥ 18 years, with septic shock, < 12 hours since ICU admission N = 45
Barzegar 2017[14]	Iran/ 3	Randomized, open-label, parallel	NE titrated to MAP ≥ 65 mm Hg +/- AVP 0.03 U/min	Sepsis biomarkers	28 days	Patients ≥ 18 years, with septic shock, < 12 hours since ICU admission N = 45

*AVP: Arginine Vasopressin, NE: Norepinephrine, MAP: mean arterial pressure, HCT: hydrocortisone phosphate

+HCT dose used: 50 mg every 6 hours or five days, then every 12 hours for three days, and once daily for three days

Review Strategy

Prospective, randomized, controlled trials are the gold standard to evaluate efficacy of an intervention. An increase in MAP is considered an acceptable measure of efficacy of

[11] Gordon AC, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med. 2014b;42(6):1325-33. PMID: 24557425

[12] Gordon AC, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18. PMID: 27483065

[13] Barzegar E, et al. The Therapeutic Role of Vasopressin on Improving Lactate Clearance During and After Vasogenic Shock: Microcirculation, Is It The Black Box? Acta Med Iran. 2016;54(1):15-23.PMID: 26853286

[14] Barzegar E, et al. Vasopressin in septic shock; assessment of sepsis biomarkers: A randomized, controlled trial. Indian Journal of Critical Care Medicine. 2017;21(9):578-84. PMID: 28970657

vasopressors. Hence, to support efficacy, 2 prospective, randomized trials that evaluated the use of AVP on background therapy with NE and provided data on change in MAP (Barzegar 2016, Barzegar 2017) were reviewed in detail. The review briefly summarizes other clinical studies submitted to support the efficacy of Vasopressin Injection.

5. Review of Relevant Individual Trials Used to Support Efficacy

Barzegar 2016

Trial Design Overview and Objectives

Barzegar 2016 is a prospective, randomized, controlled, open-label trial that evaluated the effect of early initiation of low-dose AVP (0.03 U/min) on the level and clearance of lactate as a marker of tissue perfusion in septic shock. Eligible patients were randomized to receive NE infusion titrated to achieve MAP ≥ 65 mm Hg or NE titrated to achieve MAP ≥ 65 mm Hg plus AVP infusion at a constant rate of 0.03 units/min (Exir Pharmaceutical Co. Tehran, Iran). Additional use of vasopressors (dopamine or epinephrine), inotropic agents (dobutamine), and HCT was at the discretion of the treating physician. No between group cross overs were permitted.

The trial was conducted between November 2012 and April 2014, in a 20-bed general surgical and emergency intensive care unit (ICU) of a tertiary teaching hospital (Sina hospital) in Tehran, Iran. The trial was approved by the Medical Ethics Committee of Tehran University of Medical Sciences (TUMS) (91-02-33-18310-63707) and a written informed consent was obtained from patients' next of kin.

Trial Endpoints

Primary endpoint: To compare venous lactate levels and lactate clearance at 24- and 48-hours between the two treatment arms.

Secondary endpoints: To compare hemodynamic parameters, arterial pH, NE requirements, mortality rate (ICU and 28-day mortality), and sepsis-related organ failure (SOFA) score between the two treatment arms.

Inclusion / Exclusion Criteria

Inclusion Criteria

The following patients were included in the trial:

- age > 18 years
- within 12 hours of diagnosis of septic shock as defined by the American college of chest physicians/society of critical care medicine consensus conference committee (two or more of Systemic Inflammatory Response Syndrome (SIRS)

criteria, infection [proven or suspected], new organ failure and hypotension)

Exclusion Criteria

- more than 12 hours of septic shock diagnosis
- previous AVP use
- mesenteric ischemia
- acute coronary syndrome
- heart failure (New York Heart Association class III or IV)
- hyponatremia (Na < 130 mmol/L)
- pregnancy
- patient with poor prognosis (death anticipated within hours), end-stage renal failure, vasospastic diseases
- recruitment in another clinical trial
- unwillingness to give written informed consent

Study Drug Discontinuation / Stopping Rules

Vasopressors were tapered off if the target MAP was maintained for more than 8 hours. AVP infusion was discontinued for shock resolution, or occurrence of life-threatening adverse events (digital ischemia, mesenteric ischemia, arrhythmias, serum sodium less than 130 mEq/ml), or patient death.

Study Schedule of Assessments

The following parameters were recorded / monitored during the trial:

- Baseline subject demographics and co-morbidities
- Baseline Simplified Acute Physiologic Score (SAPS) II for assessment of severity of illness
- Baseline and daily record of SOFA score as marker of organ dysfunction
- Continuous monitoring (per ICU protocol) of hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, central venous pressure (CVP), body temperature and oxygen saturation
- Baseline, 24- and 48-hours after randomization, serum levels of lactate, sodium, white blood cell count (WBC), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and creatinine; and arterial blood gas
- Baseline level of procalcitonin
- Baseline and daily electrocardiogram
- As clinically indicated, cardiac enzymes, echocardiogram, and other diagnostic imaging
- During ICU admission and 28 days after randomization, survival status

- Daily monitoring of adverse events
- Daily NE requirement

Statistical Analysis

The study had an 80% power to detect a 1.6 mmol/L difference in lactate levels at 24 and 48 hours at a significance level of 0.05. A standard deviation of 1.6 mmol/l in lactate level was assumed.

Patient disposition

A total of 30 patients who met the eligibility criteria were randomly assigned to NE or NE+AVP arm and completed the trial.

Results

There were no significant differences in the baseline demographic and clinical characteristics of subjects between the two treatment arms. There were no significant differences in the lactate level at 24- and 48-hours between the two arms - NE vs. AVP+NE (28.4 vs. 23.1 mg/dl, P=0.67 and 15.8 vs. 10.3 mg/dl, *P*=0.47, respectively). Lactate clearance at 24-hours was lower in NE compared to AVP+NE arm (21 vs. 46%, P=0.048), and at 48-hours was not different between the two arms.

Baseline hemodynamic parameters were comparable between the two treatment arms. The MAP at 24-hours was statistically significantly higher in the AVP+NE arm compared to NE arm, and at 48-hours, there was no difference between the two arms (table 3). According to the author, the NE dose requirements were lower in the NE+AVP arm, but no details were provided.

Table 3. Changes in hemodynamic parameters in Barzegar 2016 Trial[13] (Source: Published journal article)

	Baseline	*P*-value	24 hr	*P*.value	48 hr	*P*-value
HR beats/min						
NE	87.2±18	0.663	105.4±10.1	0.003	104.8±7.8	0.0001
AVP	90.2±19.2		86.9±18.9		85.1±11.1	
SBP, mm Hg						
NE	75.1±11.1	0.295	101.8±27.6	0.032	123.5±19.4	0.790
AVP	80.±14		121.9±20.3		121.5±15.6	
MAP, mm Hg						
NE	62.2±6.5	0.613	79.5±10.4	0.044	82.1±16.3	0.671
AVP	65.4±6.4		87.6±10.4		85.1±16	
CVP mm Hg H2O						
NE	11.5±11.2	0.41	17.3±6.2	0.86	11.1±9.8	0.16
AVP	15.4±4.9		16.9±5.3		16.9±4.9	

HR: heart rate, NE: norepinephrine, AVP: arginine vasopressin, SBP: systolic blood pressure, MAP: mean arterial pressure, CVP: central venous pressure

***Reviewer Comments**: Data from Barzegar 2016 trial suggest that AVP increases MAP when used in addition to NE in patients with septic shock. As this trial was not powered to evaluate a change in MAP as a primary endpoint, these results are only considered as supportive evidence of vasopressor effect of AVP.*

Barzegar 2017

Trial Design Overview and Objectives

Barzegar 2017[14] is a prospective, randomized, controlled, open-label trial that evaluated the effect of early initiation of low-dose AVP (0.03 U/min) on biomarkers of sepsis in patients with septic shock. The biomarkers evaluated in this study included interleukin-6 (IL-6), interleukin-10 (IL-10), pentraxin 3 (PTX3), angiopoietin 1 (Ang-1), and angiopoietin 2 (Ang-2). Generally, the trial design (except the endpoints), eligibility criteria, study drug discontinuation/ stopping rules, schedule of study assessments, and time period of the trial were similar to Barzegar 2016. Additional information is provided under relevant subsections.

Trial Endpoints

Primary endpoint: To compare the levels of biomarkers for sepsis between the two treatment arms.

Secondary endpoints: To compare hemodynamic parameters, NE requirements, mortality rate (ICU and 28-day mortality), organ failure, and effect of corticosteroids on the biomarkers between the two treatment arms.

Study Schedule of assessments

In addition to the study assessments mentioned under Barzegar 2016, blood samples to measure biomarkers for sepsis (IL-6, IL-10, PTX3, Ang-1, and Ang-2) were collected at baseline, 24 hrs, and 48 hrs after randomization.

Statistical Analysis

Sample size calculation is not described in the publication.

Patient disposition

A total of 45 patients who met the eligibility criteria were randomly assigned to NE or NE+AVP arm, and 42 subjects completed the trial.

Results

There were no significant differences in the baseline demographic and clinical characteristics of subjects between the two treatment arms. There were no significant differences in the levels of biomarkers for sepsis at 24- and 48-hours between the two arms - NE vs. AVP+NE.

Baseline hemodynamic parameters were comparable between the two treatment arms. The MAP at 24-hours was statistically significantly higher in the AVP+NE arm compared to NE arm, and at 48-hours, there was no difference between the two arms (table 4). At 24- and 48-hours, the heart rate and dose requirements for NE were lower in the NE+AVP arm (table 4).

Table 4. Changes in Hemodynamic Parameters and NE Infusion rate in Trial Barzegar 2017[14] (Source: Published journal article)

	Baseline	*P*	24 h	*P*	48 h	*P*
HR (beats/min)						
NE	87.1±18.5	0.76	105±10.2	0.001	106.8±8.1	0.001
AVP	89.8±18		85.4±16.2		87.2±10.1	
SBP (mmHg)						
NE	75.7±11.1	0.73	98.2±31.3	0.002	120.1±18.8	0.40
AVP	77±12.8		124.4±18.6		125.5±18.5	
MAP (mmHg)						
NE	62.1±6.2	0.32	77.8±12.7	0.008	74±22	0.10
AVP	64.1±6.4		87.3±9		84.4±14.6	
CVP (mmHg H_2O)						
NE	10.1±11.2	0.67	16.3±5.4	0.90	12.3±8.5	0.10
AVP	11.7±8.1		16.5±4.9		16.7±5	
Creatinine (mg/dl)						
NE	1.4±0.5	0.42	1.6±0.4	0.22	1.7±0.9	0.29
AVP	1.3±0.6		1.4±0.6		1.4±0.7	
NE infusion rate (µg/min)						
NE	12.7±4.2	0.62	13.5±5.6	0.001	8.3±4.5	0.013
AVP	13.3±4.3		5.2±4		4.5±3.8	

***Reviewer Comments**: Similar to Barzegar 2016, data from Barzegar 2017 trial suggest that AVP increases MAP when used in addition to NE in patients with septic shock. As this trial was not powered to evaluate a change in MAP as a primary endpoint, these results are only considered as supportive evidence of vasopressor effect of AVP.*

Other Studies to Support Efficacy

Gordon 2014[11] and **Gordon 2016[12]** utilized AVP as background therapy to evaluate the effects of HCT versus placebo on level of AVP and renal outcomes, respectively. Hence, these studies are not informative on the effect of AVP on MAP on background therapy with catecholamines.

Hammond 2018[15] was a single-center, open-label trial that compared the time to achieve and maintain a target MAP of 65 mm Hg between NE + AVP, versus NE alone. Hammond 2018 demonstrated that use of NE+AVP significantly decreased the time to achieve and maintain the

[15]Hammond DA, et al. Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock. Pharmacotherapy. 2018;38(5):531-8. PMID: 29600824

target MAP (5.7 hours (interquartile range [IQR] 1.7–10.3 hrs), compared with 7.6 hours (IQR 3.6–16.7 hrs, p=0.058). However, data on changes in MAP was not provided.

Buckley 2017[16] was a retrospective cohort study evaluating the catecholamine-sparing effect of AVP at 0.04 units/min and/or HCT in patients with septic shock and demonstrated that concomitant AVP and HCT was associated with additive catecholamine-sparing effect compared to either agent alone.

Hajjar 2017[17] was a prospective, randomized, double-blind trial evaluating the effect of AVP versus NE administered to maintain MAP, on mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure) within 30 days in patients with vasoplegic shock after cardiac surgery. Hajjar 2017 enrolled 330 patients and demonstrated that the incidence of mortality or severe complications was lower in the AVP versus NE arm 32 %; 95% CI, 24.7 to 39.7 versus 49%; 95% CI, 41.0 to 57.0 (adjusted hazard ratio, 0.52; 95% CI, 0.36 to 0.75; *P* = 0.0005). With AVP, the median MAP increased from 55 (50-60) mm Hg at baseline to 73 (70-77) mm Hg at 12 hours post infusion. The increase in MAP was similar between the AVP and NE arms.

Nguyen 2017[18] and **Ohsugi 2019**[19] are retrospective studies that evaluated the effect of a second vasoactive agent in patients with septic shock receiving NE on mortality and demonstrated that AVP did not decrease mortality in patients with septic shock.

Published literature pertaining to any pediatric age group was not reviewed.

Reviewer Comments: *These studies have several study design limitations and confounding factors that limit the conclusions that can be drawn about the effect of AVP on MAP in patients with septic shock unresponsive to fluids and catecholamines.*

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[16] Buckley MS, et al. Concomitant vasopressin and hydrocortisone therapy on short-term hemodynamic effects and vasopressor requirements in refractory septic shock. Journal of Critical Care. 2017;42:6-11.

[17] Hajjar LA, et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. Anesthesiology. 2017;126(1):85-93. PMID: 27841822. https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/ALN/B/ALN_2016_10_07_HAJJAR_ALN-D-16-00041_SDC1.pdf

[18] Nguyen HB, et al. Comparative Effectiveness of Second Vasoactive Agents in Septic Shock Refractory to Norepinephrine. J Intensive Care Med. 2017;32(7):451-9. PMID: 27189952

[19] Ohsugi K, et al. Does vasopressin improve the mortality of septic shock patients treated with high-dose NA. Indian J Crit Care Med. 2016;20(3):137-40. PMID: 27076723

6. Review of Safety

Safety Review Approach

To support safety of AVP, 8 published studies, 15 case reports, and adverse event reports from the applicant's post-marketing surveillance database and the FDA adverse event reporting system, were reviewed. No patient-level data were provided. The sources of safety data did not distinguish between serious adverse events (SAEs) or adverse events (AEs).

Review of the Safety Database

Overall Exposure

Overall, 2,255 adult subjects were exposed to 0.01 to 0.08 U/min of IV AVP infusion titrated to a MAP ≥ 65 mm Hg for a duration ranging between ≤ 24 hours to > 48 hours in 14 clinical studies reported in the literature. A precise average duration of AVP infusion could not be determined from the published literature.

Safety Results

Controlled Clinical Trials

Table 5 displays the AEs reported by five controlled clinical trials of AVP, 5 in adult subjects (Gordon 2014, Gordon 2016, Barzegar 2016, Hajjar 2017), and 1 in pediatric subjects (Rios 2015). The overall incidence of reported AEs in these trials was 17.5% in the AVP arm versus 15.0% in the comparator arm (dopamine or NE or NE/HCT). The most common AEs with an incidence of > 1% and reported at a higher rate in the AVP arm, were hyponatremia (3.7%), digital ischemia (3.2%), mesenteric ischemia (1.7%), and acute coronary syndrome (1.5%).

Gordon 2014 compared AVP+HCT versus AVP+placebo and reported a total of 14 AEs, included in the summary table 5. These AEs were extension of a pre-existing recent ischemic cerebral infarct (n=1), cool/mottled peripheries (n=4), rise in serum lactate (n=1), and rise in troponin (n=1).

***Reviewer Comments**: In Gordon 2014 trial, all subjects received AVP. As there was no comparator to AVP and the AEs were not reported by study arm, counting these events in summary table 5, bias the finding of AEs toward the AVP arm.*

Barzegar 2017 reported that rate of AEs (arrhythmia, digital ischemia,

and hyponatremia) was similar in both groups but these rates were not reported

and not counted in summary table 5.

Hajjar 2017 was a controlled trial of subjects with vasoplegic shock after cardiac surgery and found a lower occurrence of atrial fibrillation (AF) in the AVP versus NE group (63.8% vs. 82.1%; P < 0.001). There was no difference in the rates of digital ischemia, mesenteric ischemia, hyponatremia, or myocardial infarction between the two groups.

There was no difference in in-hospital, 28-day, or 30-day mortality rates between AVP and comparator groups in trials - Gordon 2014, Gordon 2016, Barzegar 2016, Barzegar 2018, Hammond 2018, and Hajjar 2017.

Rios 2015 enrolled 20 hypotensive infants who received AVP (n=10) or dopamine (n=10) and reported 4/10 deaths in the AVP arm and 2/10 deaths in the comparator arm . No other AEs were reported in the Rios 2015 publication.

Table 5. Adverse events reported in controlled clinical trials of Vasopressin by study arms (Source: Applicant table 4, page 11 of the summary of clinical safety)

	Vasopressin (rate ranges)			Comparators			
Body System/Adverse Event	**< 0.04 (U/min) (Rios, 2015; Barzegar, 2016; Barzegar 2017) n = 48 (13%)**	**> 0.04 (U/min) (Gordon, 2016; Gordon, 2014; Hajjar, 2017) n = 415 (90%)**	**Total (%) n = 463**	**Dopamine 5 mcg/kg/min (Rios 2015) n = 10 (2.3%)**	**NE 5-60 µg/min (Barzegar 2016; Gordon, 2016, Hajjar, 2017, Barzegar 2017) n = 307 (73.3%)**	**NE/HCT 12 µg/min/ 200 mg/day (Gordon 2016) n = 102 (24.4%)**	**Total (%) n = 419**
Acute coronary syndrome	0	7 (1.7%)	7 (1.5%)	0	0	2 (2.0%)	2 (0.4%)
Arrhythmia	1 (2%)	0	1(0.2%)	0	3 (1.0%)	0	3 (0.6%)
Cardiac arrest	1 (2%)	0	1 (0.2%)		3 (1.0%)	0	3 (0.6%)
Life-threatening arrhythmia	0	2 (0.5%)	2 (0.4%)	0	4 (1.3%)	1 (1.0%)	5 (1.2%)
Post-operative acute myocardial infarction	0	11 (2.7%)	11 (2.4%)	0	17 (5.5%)	0	17 (3.3%)
Hyponatremia	5 (10.4%)	12 (2.9%)	17 (3.7%)	3 (30%)	10 (3.3%)	0	13 (2.1%)
Hyperglycemia	3 (6.3%)	0	3 (0.6%)	2 (20%)	0	0	2 (0.4%)
Cool/mottled peripheries	0	3 (0.7%)	3 (0.6%)	0	0	0	0
Extension of a preexisting recent ischemic cerebral infarct	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Rise in serum lactate	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Rise in troponin	0	1 (0.24%)	1 (0.2%)	0	0	0	0
Digital ischemia	1 (2%)	14 (3.4%)	15 (3.2%)	0	3 (1.0%)	2 (2.0%)	5 (0.4%)
Mesenteric ischemia	0	8 (1.9%)	8 (1.7%)	0	3 (1.0%)	4 (4.0%)	7 (1.3%)
Hypertension	2	0	2 (0.4%)	0	0	0	0
Other	0	4 (1.0%)	4 (0.9%)	0	1 (0.33%)	3 (3.0%)	4 (0.8%)
Death	4 (8.3%)	0	4 (0.9%)	2 (20%)	0	0	2 (0.4%)
Totals	17 (35.4%)	64 (15.4%)	81(17.5%)	7 (70%)	44 (14.3%)	12 (11.8%)	63 (15.0%)

Reviewer Comments: *The applicant summary table 5 is limited by 1) lack of comparator arm in Gordon 2014 trial, 2) incomplete reporting of AEs Barzegar 2017, 3) inclusion of a pediatric study (Rios 2015), and 4) varied study designs and comparators. The label of the RLD and the proposed label states that "the most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital)." The AEs reported in the published controlled clinical trials submitted by the applicant are consistent with FDA's previous findings of safety with the RLD. Hence, no labeling change is indicated for section 6 Adverse Reactions.*

Observational Studies

Table 6 displays the AEs with AVP reported in three observational studies (Reardon 2014, Anantasit 2014, and Bissell 2015). The overall incidence of reported AEs was 19% in the AVP arm versus 11.9% in the comparator arm (NE or HCT). The most common AEs with an incidence of > 1% and reported at a higher rate in the AVP arm were AF (4.3%), ventricular tachycardia (2.5%), myocardial ischemia (2.5%), mesenteric ischemia (1.6%), and arrhythmia (1.6%). The label for Vasostrict describes AF, and tachyarrhythmias as adverse reactions.

Table 6. Adverse events reported in observational studies of Vasopressin by study arms (Source: Applicant table 5, page 14 of the summary of clinical safety)

	Vasopressin	Comparators		
Body System/Adverse Event	Ranges 0.01-0.04 (U/min) (Reardon, 2014; Anantasit, 2014; Bissell 2015) n = 516	NE 5-15 µg/min (Anantasit, 2014) n = 715	HCT 200 mg/day (Bissell, 2015) n = 31	Total (%) n = 746
Arrhythmia	8 (1.6%)	0	5 (16%)	5 (0.67%)
Cardiac arrest	2 (0.39%)	0	0	0
Atrial fibrillation	22 (4.3%)	0	0	0
Bradyarrhythmia	6 (1.2%)	11 (1.5%)	0	11 (1.5%)
Tachyarrhythmia	5 (0.97%)	15 (2.1%)	0	15 (2.0%)
Ventricular fibrillation	1 (0.2%)	0	0	0
Ventricular tachycardia	13 (2.5%)	0	0	0
Hyponatremia	3 (0.6%)	1 (0.14%)	4 (13%)	5 (0.67%)
Hyperglycemia	6 (1.2%)	0	9 (29%)	9 (1.2%)
Superinfection	1 (0.2%)	0	10 (32%)	10 (1.3%)
Digital ischemia	4 (0.8%)	4 (0.6%)	0	4 (0.54%)
Mesenteric ischemia	8 (1.6%)	8 (1.1%)	0	8 (0.11%)
Myocardial ischemia	13 (2.5%)	13 (1.8%)	0	13 (1.7%)
Cerebrovascular accident	2 (0.39%)	7 (1%)	0	7 (0.93%)
Other	4 (0.8%)	2 (0.3%)	0	2 (0.27%)
Totals	98 (19%)	61 (8.5%)	28 (90%)	89 (11.9%)

Post market surveillance data

The applicant's post market surveillance adverse event data by the highest level MedDRA system organ class (SOC) categories based on its pharmacovigilance data retrieved 40 AEs, with the most common AEs (in decreasing order) being metabolic and nutrition disorders (25 %), endocrine disorders (15%), vascular disorders (12.5%), cardiac disorders (10%), general disorders and administration site conditions (7.5%), and nervous system disorders (7.5%).

The applicant's post market surveillance adverse event data by highest level MedDRA system organ class (SOC) categories based on FDA Adverse Event Reporting System (FAERs) database retrieved 740 AEs with the most common AEs (in decreasing order) being general disorders and administration site conditions (n=176, 23.78%), product issues (n=137, 18.51%), cardiac disorders (n=122, 16.49%), renal and urinary disorders (n = 42, 5.7%), and nervous system disorders (n = 40, 5.4%).

The sponsor did not provide additional details about AEs related to product issues. An internal search of the FAERS database by OSE retrieved 67 serious reports coded with the MedDRA term "Drug ineffective" between 2013 and 2019. A review of 8 random sample case reports by OSE showed that these patients had severe conditions such as medication-overdose-induced severe metabolic acidosis, post-surgical sepsis, post-surgical cardiac arrest, vasoplegia refractory to vasopressors, flecainide toxicity, and Haemophagocytic lymphohistiocytosis mimicking sepsis. Most of these reports mention that the patient was refractory to norepinephrine and other vasopressors including vasopressin. Vasopressin has not been marketed since November 1, 2012. From the available information, it is difficult to determine if there is truly a product quality issue or a non-response to treatment due to the severity of the underlying illness.

Special Populations

Pediatrics: The efficacy and safety of AVP in vasodilatory shock in pediatric patients has not been established. The applicant identified two pediatric studies (Rios 2015, Iliopoulos 2017) during the systematic review. Other than mortality, these studies did not report safety outcomes.

Geriatric Use: The clinical studies of AVP do not provide safety data based on age groups.

The applicant did not provide any additional data to inform use of AVP in pregnancy and lactation, renal or hepatic impairment, or the drug abuse potential of AVP.

Withdrawal and Rebound

Applicant's systematic literature search revealed 10 case reports of transient diabetes insipidus (DI) after discontinuation of AVP infusion. DI was treated with re-initiation of AVP and/or Desmopressin, and fluid administration and most cases resolved within 24 -48 hours of onset of DI. In these case reports, the age range of

patients was 23 to 58 years old. indications for AVP use included septic shock, vasospasm, and acute and chronic neurological conditions; and duration of initial treatment with AVP ranged from 15 hours to 5 days.

Reviewer Comments: *The mechanism of DI after withdrawal of AVP is not well understood. Clinical presentation of transient DI after cessation of AVP infusion indicates that these may be cases of nephrogenic DI. A proposed mechanism for occurrence of nephrogenic DI is the downregulation of V2 receptors during treatment with AVP, described in literature as renal escape from antidiuresis[20].*

7. Consultations

On July 10, 2019, the Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pharmacovigilance I (DPV-I), Office of Surveillance Epidemiology (OSE) to conduct a FAERS search for post market adverse event cases with a serious outcome for adult and pediatric patients with Pitressin (vasopressin) injection from January 1, 2013 to present to help support the NDA review.

DPV-I searched the FAERS database for time period of January 1, 2013 – September 17, 2019. This search retrieved 270 and 60 reports for vasopressin with a serious outcome and death, respectively. In reports of serious outcome, that provided patient's age, there were 185 reports for adults and 35 reports for pediatric age group.

In adults with reports with a serious outcome, the most frequently reported MedDRA Preferred Term (PT) AEs were drug ineffective (n=67), hypotension (n=33), DI (n=19), and shock (n=16). The PTs not currently mentioned in the label for Vasostrict included optic atrophy (n=7), blindness (n=5), blindness, cortical (n=5), optic nerve injury (n=5), retinal ischemia (n=5), and visual impairment (n=5).

To identify the presence of a new safety signal, DPV-I data mining using the Empirica Signal software for vasopressin reports with a serious outcome received by FDA. The consult states that, "*DPV-I identified cases of transient diabetes insipidus occurring upon withdrawal of vasopressin as an unexpected adverse event and a potential safety signal for DCaRP's consideration for the purpose of review of NDA 212593 (vasopressin injection).*"

Reviewer Comments: *The finding of cases of transient DI by DPV-I FAERS data analysis is consistent with the case reports of DI submitted by the sponsor. Based on the review of case reports in literature and FAERS data analysis by DPV-I, transient DI after discontinuation of vasopressin is a new safety signal and should be considered for inclusion in the label.*

[20] *Michael A. Bohl, James Forseth, Peter Nakaji. Transient Diabetes Insipidus After Discontinuation of Vasopressin in Neurological Intensive Care Unit Patients: Case Series and Literature Review. World Neurosurg. (2017) 97:479-488.*

8. Labeling Recommendations

The potential for the development of transient DI after cessation of AVP infusion should be included in the label for Vasopressin Injection, USP and the label for Vasostrict should be accordingly revised.

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/s/

CHARU GANDOTRA
12/02/2019 02:15:20 PM