Vasostrict® (vasopressin injection) for intravenous use

**INDICATIONS AND USAGE**

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

**DOSE AND ADMINISTRATION**

**Preparation of Diluted Solutions**

Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (DSW) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

**Dosage and Administration**

- Dilute Vasostrict® with normal saline (0.9% sodium chloride) or 5% dextrose in water to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

**Contraindications**

- Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

**Warnings and Precautions**

- Can worsen cardiac function. (5.1)

**Drug Interactions**

- Pressor effects of catecholamines and Vasostrict® are expected to be additive. (7.1)
- Indomethacin may prolong the effects of Vasostrict®. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

**Use in Specific Populations**

- Pregnancy: May induce uterine contractions. (8.1)
- Pediatric Use: Safety and effectiveness have not been established. (8.4)
- Geriatric Use: No safety issues have been identified in older patients. (8.5)

**Adverse Reactions**

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

**Preparation of diluted solutions**

Table 1 Preparation of diluted solutions

<table>
<thead>
<tr>
<th>Fluid restriction?</th>
<th>Final concentration</th>
<th>Mix</th>
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<tbody>
<tr>
<td>No</td>
<td>0.1 units/mL</td>
<td>2.5 mL (50 units)</td>
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<tr>
<td>Yes</td>
<td>1 unit/mL</td>
<td>5 mL (100 units)</td>
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Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

**Contraindications**

Vasostrict® is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

**Warnings and Precautions**

- Worsening Cardiac Function
  - Use in patients with impaired cardiac response may worsen cardiac output.

**Adverse Reactions**

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

- Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding
- Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia
- Gastrointestinal disorders: Mesenteric ischemia
- Hepatobiliary: Increased bilirubin levels
- Renal/urinary disorders: Acute renal insufficiency
- Vascular disorders: Distal limb ischemia
- Metabolic: Hyponatremia
- Skin: Ischemic lesions

**Drug Interactions**

- Catecholamines
  - Use with catecholamines is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

- Indomethacin
  - Use with indomethacin may prolong the effect of Vasostrict® on cardiac index and systemic vascular resistance [see Clinical Pharmacology (12.3)].

- Ganglionic Blocking Agents
  - Use with ganglionic blocking agents may increase the effect of Vasostrict® on mean arterial blood pressure [see Clinical Pharmacology (12.3)].

- Furosemide
  - Use with furosemide increases the effect of Vasostrict® on osmolar clearance and urine flow [see Clinical Pharmacology (12.3)].
Clinical Considerations: It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman. There are no adequate or well-controlled studies of Vasostrict® in pregnant women. Pregnancy Category C. 8.1 Pregnancy. 8.2 Use in Specific Populations. 8.3 Nursing Mothers. It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Safety and effectiveness of Vasostrict® in pediatric patients with vasodilatory shock have not been established. 8.4 Pediatric Use. 8.5 Geriatric Use. Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Hepatic Impairment. 8.7 Renal Impairment. 8.8 Cardiac Impairment. 8.9 Drug Exposures. 8.10 Dosage Forms. 8.11 How Supplied/Storage and Handling. 11 DESCRIPTION. Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8. The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyll-L-Prolyll-L-Arginyll-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:

\[
\text{H-Cys-Tyr-Phc-Glu(NH}_2\text{)}_3 - \text{Asp(NH}_2\text{)}_2 - \text{Cys-Pro-Arg-Gly-NH}_2
\]

Molecular Formula: \(C_{66}H_{115}N_{15}O_{13}S_2\) Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY. 12.1 Mechanism of Action. The vasoconstrictive effects of vasopressin are mediated by vascular V1 receptors. Vascular V1 receptors are directly coupled to phospholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V2 receptors which are coupled to adenyl cyclase. 12.2 Pharmacodynamics. At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V1 receptors and release of prolactin and ACTH via V2 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients. 12.3 Pharmacokinetics. At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent t1/2 of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxide-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions. Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects [see Drug Interactions (7.2)]. The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects [see Drug Interactions (7.3)]. Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects [see Drug Interactions (7.4)]. Halothane, morphine, fentanyl, alfentanil and sufentanil do not impact exposure to endogenous vasopressin.

Special Populations. Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks. 13 NONCLINICAL TOXICOLOGY. 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the in vitro bacterial mutagenicity (Ames) test and the in vitro Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertility of spermatogenesis.

14 CLINICAL STUDIES. Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock. 16 HOW SUPPLIED/STORAGE AND HANDLING. Vasostrict® (vasopressin injection, USP) is supplied in vials as follows: A carton of 25 single dose vials containing vasopressin 1 mL at 20 units/mL. Store between 2°C and 8°C (36°F and 46°F). Do not freeze. Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial. The storage conditions and expiration periods are summarized in the following table.

<table>
<thead>
<tr>
<th>NDC 42023-164-25 (carton)</th>
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<tbody>
<tr>
<td>Distributed by:</td>
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<tr>
<td>Par Pharmaceutical Companies, Inc.</td>
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