HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VASOSTRICT® safely and effectively. See full prescribing information for VASOSTRICT®.

VASOSTRICT® (vasopressin injection) for intravenous use

Initial U.S. Approval: 2014

Contraindications (4) 03/2019

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

- Can worsen cardiac function. (5.1)

- Pressor effects of catecholamines and Vasostrict® are expected to be additive. (7.1)

- 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)

- 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)

FULL PRESCRIBING INFORMATION

1 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.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

<table>
<thead>
<tr>
<th>Fluid restriction?</th>
<th>Final concentration</th>
<th>Mix</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.1 units/mL</td>
<td>2.5 mL (50 units)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 unit/mL</td>
<td>5 mL (100 units)</td>
</tr>
</tbody>
</table>

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

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute to 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

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

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

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

7.2 Indomethacin

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

7.3 Ganglionic Blocking Agents

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

7.4 Furosemide

Use with furosemide increases the effect of Vasostrict® on osmolar clearance and urine flow [see Clinical Pharmacology (12.3)].

* Sections or subsections omitted from the full prescribing information are not listed.
7.5 Drugs Suspected of Causing SIADH
Use with drugs suspected of causing SIADH (e.g., SSRIs, tricyclic antidepressants, haloperidol, clonazepam, enalapril, methyldopa, pramartine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict®.

7.6 Drugs Suspected of Causing Diabetes Insipidus
Use with drugs suspected of causing diabetes insipidus (e.g., demeclocycline, lithium, foscarin, clozapine) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C
Risk Summary: There are no adequate or well-controlled studies of Vasostrict® in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin (see Clinical Pharmacology (12.3)).

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict® may need to be up-titrated to doses exceeding 0.1 units/min in post-cardiotomy shock and 0.07 units/min in septic shock. Vasostrict® may produce tonic uterine contractions that could threaten the continuation of pregnancy.

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. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use
Safety and effectiveness of Vasostrict® in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use
Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)].

10 OVERDOSAGE
Overdose with Vasostrict® can be expected to manifest as consequences of vasocostriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdose may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms. Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION
Vasopressin is a polypeptide hormone 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 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.6. The 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8. The chemical name of vasopressin is Cyclo (-6) L-Cysteinyl-L-Tyrsoyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:

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

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 phopholipase C, resulting in release of calcium, leading to vasocostriction. In addition, vasopressin stimulates antidiuresis via stimulation of V₂ receptors which are coupled to adenylyl cyclase.

12.2 Pharmacodynamics
At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchic, 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 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 noradrenaline. 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 vasodilator shock (0.01-0.1 units/min) the clearance of vasopressin is 0.25 ml/min in humans. The clearance 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 mediated via renal metabolism. There is no evidence for a metabolite that is active as vasopressin.

The volume of distribution of exogenous 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 mutageneity (Ames) test and the in vitro Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

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.

14.1 HOW SUPPLIED/STORAGE AND HANDLING
Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as:

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

NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (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 label expiration date. When 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 expiry date as indicated on the label.

After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrgerated 10 mL vial after 30 days after first puncture.

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

<table>
<thead>
<tr>
<th>Storage Conditions</th>
<th>Expiration Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopened Refrigerated</td>
<td>2°C to 8°C (36°F to 46°F)</td>
</tr>
<tr>
<td>Unopened Room Temperature</td>
<td>20°C to 25°C (68°F to 77°F)</td>
</tr>
</tbody>
</table>

| Unopened Refrigerated | 2°C to 8°C (36°F to 46°F) |
| Unopened Room Temperature | 20°C to 25°C (68°F to 77°F) |

<table>
<thead>
<tr>
<th>Opened (After First Puncture)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>1 mL Vial</th>
<th>10 mL Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Until manufacturer expiration date</td>
<td>Until manufacturer expiration date, whichever is earlier</td>
</tr>
<tr>
<td>12 months or until manufacturer expiration date, whichever is earlier</td>
<td>12 months or until manufacturer expiration date, whichever is earlier</td>
</tr>
<tr>
<td>30 days</td>
<td>30 days</td>
</tr>
</tbody>
</table>

Distributed by: Par Pharmaceutical
Chesnut Ridge, NY 10977

R03/19
OS164J-01-90-09

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