

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212593Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **VASOPRESSIN INJECTION** safely and effectively. See full prescribing information for **VASOPRESSIN INJECTION**.

VASOPRESSIN injection, for intravenous use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

- Vasopressin injection is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines. (1)

DOSAGE AND ADMINISTRATION

- Dilute vasopressin injection with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) 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)

DOSAGE FORMS AND STRENGTHS

- Injection: 20 units per mL. (3)

CONTRAINDICATIONS

- Vasopressin injection 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)
- Reversible diabetes insipidus (5.2)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Pressor effects of catecholamines and vasopressin injection are expected to be additive. (7.1)
- Indomethacin may prolong effects of vasopressin injection. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH (syndrome of inappropriate antidiuretic hormone secretion) may increase the pressor response. (7.3, 7.4)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.5)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May induce tonic 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)

Revised: 8/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasopressin injection is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute vasopressin injection 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 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasopressin Injection	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

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

2.2 Administration

In general, titrate to the lowest dose compatible with a clinically acceptable response.

The recommended starting dose is:

Post-cardiotomy shock: 0.03 units/minute

Septic Shock: 0.01 units/minute

Titrate up by 0.005 units/minute at 10- to 15-minute intervals until the target blood pressure is reached. There are limited data for doses above 0.1 units/minute for post-cardiotomy shock and 0.07 units/minute for septic shock. Adverse reactions are expected to increase with higher doses.

After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper vasopressin injection by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Vasopressin injection, USP is a clear, colorless solution available as 20 units/mL in a single-dose vial.

4 CONTRAINDICATIONS

Vasopressin injection is contraindicated only in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

A decrease in cardiac index may be observed with use of vasopressin.

5.2 Reversible Diabetes Insipidus

Patients may experience reversible diabetes insipidus, manifested by the development of polyuria, a dilute urine, and hypernatremia, after cessation of treatment with vasopressin. Monitor serum electrolytes, fluid status, and urine output after vasopressin discontinuation. Some patients may require readministration of vasopressin or administration of desmopressin to correct fluid and electrolyte shifts.

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

Postmarketing Experience

Reversible diabetes insipidus [*see Warnings and Precautions (5.2)*].

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. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of vasopressin injection on cardiac index and systemic vascular resistance. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed [see *Clinical Pharmacology (12.3)*].

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of vasopressin injection on mean arterial blood pressure. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed [see *Clinical Pharmacology (12.3)*].

7.4 Drugs Suspected of Causing SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion)

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of vasopressin injection. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

7.5 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of vasopressin injection. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on vasopressin injection use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with vasopressin.

Clinical Considerations

Dose Adjustments during Pregnancy and the Postpartum Period

Because of increased clearance of vasopressin in the second and third trimester, the dose of vasopressin injection may need to be increased [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

Maternal adverse reactions

Vasopressin injection may produce tonic uterine contractions. Vasopressin receptors are present in human uterine muscle and might not be distinguishable from oxytocin receptors.

8.2 Lactation

Risk Summary

There are no data on the presence of vasopressin injection in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness of vasopressin injection 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* (5.1, 5.2), *Adverse Reactions* (6), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

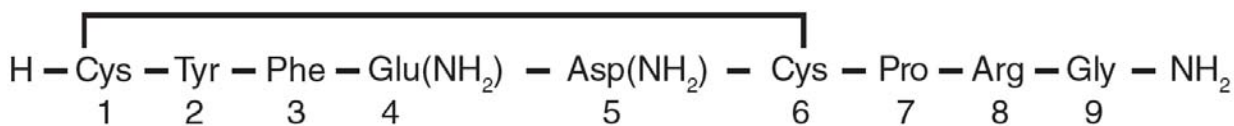
Overdosage with vasopressin injection can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone. Vasopressin injection is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units, chlorobutanol 5 mg, sodium chloride 9 mg, water for injection, and acetic acid to adjust pH to 3.5.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-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:



Molecular Formula: C₄₆H₆₅N₁₅O₁₂S₂

Molecular Weight: 1084.23

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vasopressin causes vasoconstriction by binding to V₁ receptors on vascular smooth muscle coupled to the Gq/11-phospholipase C-phosphatidyl-inositol-triphosphate pathway, resulting in the release of intracellular calcium. 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 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, ACTH and catecholamines via V₃ receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V₂ receptors. In addition, vasopressin has been demonstrated to cause vasodilation in numerous vascular beds that is mediated by V₂, V₃, oxytocin and purinergic P₂ 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. The pressor effect reaches its peak 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

Vasopressin plasma concentrations increase linearly with increasing infusion rates from 10 to 200 µU/kg/min. Steady state plasma concentrations are achieved after 30 minutes of continuous intravenous infusion.

Distribution

Vasopressin does not appear to bind plasma protein. The volume of distribution is 140 mL/kg.

Elimination

At infusion rates used in vasodilatory shock (0.01 to 0.1 units/minute), the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent t_{1/2} of vasopressin at these levels is ≤10 minutes.

Metabolism

Serine protease, carboxipeptidase and disulfide oxido-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.

Excretion

Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged into urine.

Specific Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase, the clearance of exogenous and 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.

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)*].

Halothane, morphine, fentanyl, alfentanil and sufentanil do not impact exposure to endogenous vasopressin.

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 sperm function, including motility, fertilization and embryonic development.

13.2. Animal Toxicology and/or Pharmacology

No toxicology studies were conducted with vasopressin.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 studies in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasopressin injection, USP is a clear, practically colorless solution for intravenous administration available as:

NDC 0517-1020-25: A carton of 25 single-dose vials each containing vasopressin 1 mL at 20 units/mL.

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Storage is permitted for up to 12 months at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F) within the expiry date. Once removed from refrigeration, mark the unopened vial with the revised 12-month expiration date. Do not return Vasopressin to the refrigerator after it has been stored at room temperature.

Discard the product after 12 months at room temperature or at the expiry date, whichever is earlier.

The storage conditions and expiration periods are summarized in the following 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)
Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier

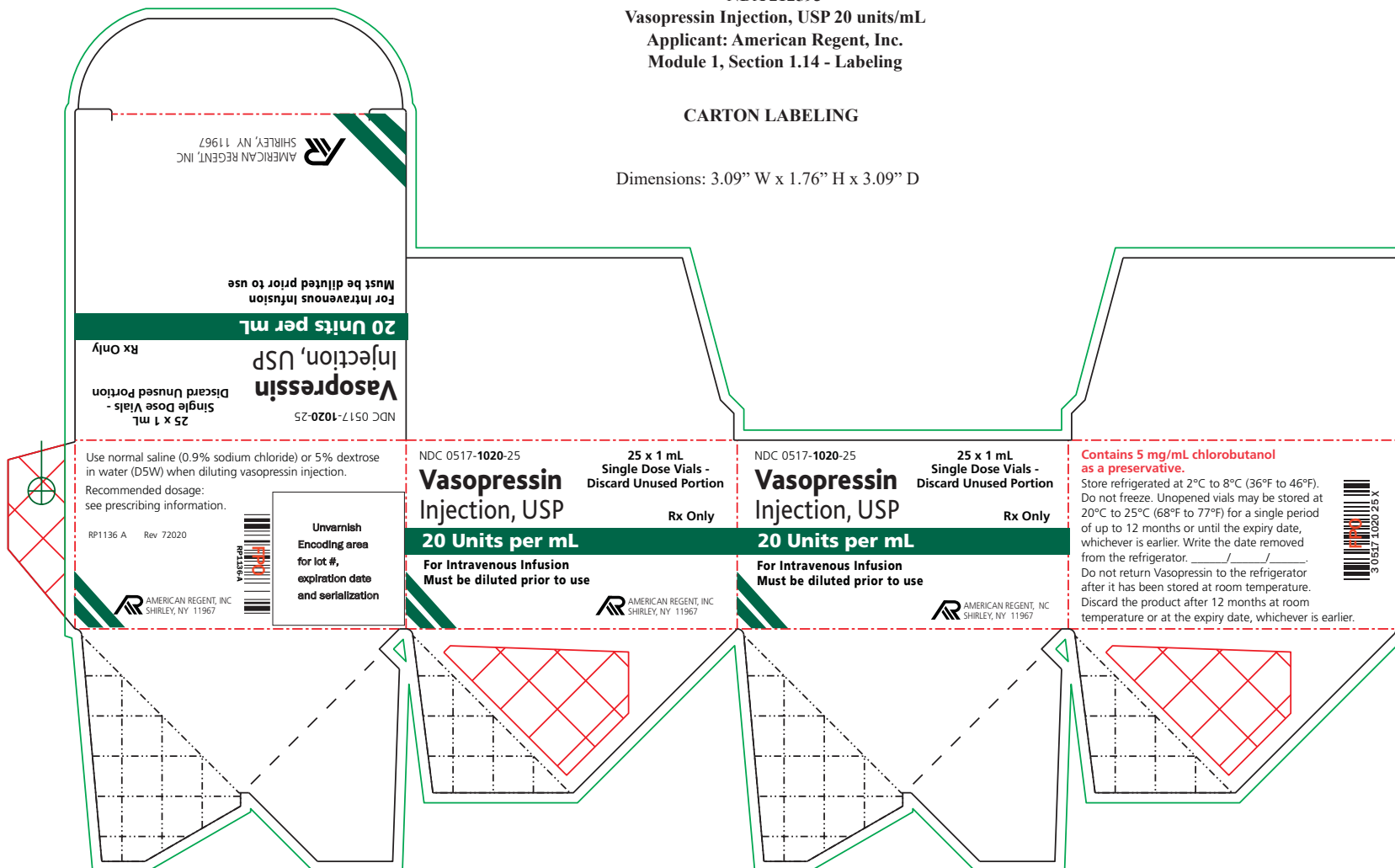
American Regent, Inc.
Shirley, NY 11967

RQ1093-A

NDA 212593
Vasopressin Injection, USP 20 units/mL
Applicant: American Regent, Inc.
Module 1, Section 1.14 - Labeling

CARTON LABELING

Dimensions: 3.09" W x 1.76" H x 3.09" D



AMERICAN REGENT, INC.
SHIRLEY, NY 11967

For Intravenous Infusion
Must be diluted prior to use

20 Units per mL
Vasopressin
Injection, USP
Rx Only
Single Dose Vials -
Discard Unused Portion
25 x 1 mL
NDC 0517-1020-25

Use normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) when diluting vasopressin injection.

Recommended dosage: see prescribing information.

RP1136 A Rev 72020

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

Unvarnish
Encoding area
for lot #,
expiration date
and serialization

NDC 0517-1020-25
25 x 1 mL
Single Dose Vials -
Discard Unused Portion
Vasopressin
Injection, USP
Rx Only

20 Units per mL
For Intravenous Infusion
Must be diluted prior to use

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

NDC 0517-1020-25
25 x 1 mL
Single Dose Vials -
Discard Unused Portion
Vasopressin
Injection, USP
Rx Only

20 Units per mL
For Intravenous Infusion
Must be diluted prior to use

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

Contains 5 mg/mL chlorobutanol as a preservative.

Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Unopened vials may be stored at 20°C to 25°C (68°F to 77°F) for a single period of up to 12 months or until the expiry date, whichever is earlier. Write the date removed from the refrigerator. Do not return Vasopressin to the refrigerator after it has been stored at room temperature. Discard the product after 12 months at room temperature or at the expiry date, whichever is earlier.

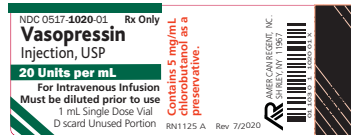
3 0517 1020 25 X

NDA 212593
Vasopressin Injection, USP 20 units/mL
Applicant: American Regent, Inc.
Module 1, Section 1.14 - Labeling

CONTAINER LABEL

Dimensions: 1.8125" W x .6858" H

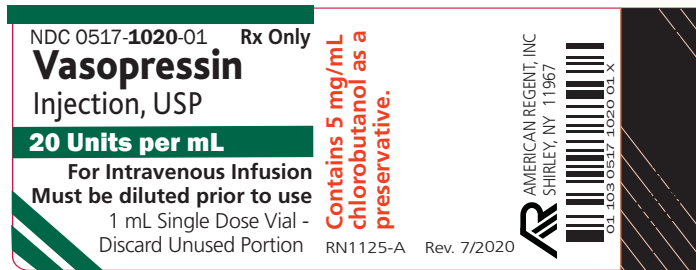
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200%

(Enlarged for Ease of Review)



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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/

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