

VASOPRESSIN- vasopressin injection, solution

American Regent, Inc.

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/ mL in a single-dose vial and 200 units/10 mL (20 units/mL) in a multiple-dose vial. (3)

CONTRAINDICATIONS

- Vasopressin injection 1 mL single-dose vial and 10 mL multiple-dose vial are 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, contact 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: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

2.2 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

5.2 Reversible Diabetes Insipidus

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

7.1 Catecholamines

7.2 Indomethacin

7.3 Ganglionic Blocking Agents

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

7.5 Drugs Suspected of Causing Diabetes Insipidus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

* Sections or subsections omitted from the full prescribing information are not listed.

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

Inspect parenteral drug products for particulate matter and discoloration prior to use,

whenever solution and container permit.

Vasopressin Injection Solution for Dilution, 20 units/mL and 200 units/10 mL (20 units/mL).

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

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, 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

Vasopressin injection 1 mL single-dose vial and 10 mL multiple-dose vial are contraindicated in patients with 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 muscles 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

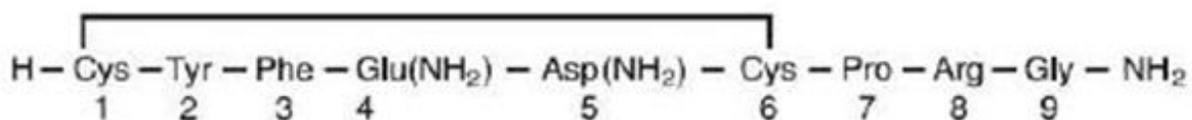
Overdosage with vasopressin injection can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, 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 administration. The 1 mL and 10 mL solution contains vasopressin 20 units/mL, chlorobutanol 5 mg, sodium chloride 9 mg, water for injection, and glacial acetic acid to adjust pH to 3.5.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyll-L-Tyrosyll-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyll-L-Prolyll-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 V_1 -receptors and release of prolactin, ACTH and catecholamines via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors. In addition, vasopressin has been demonstrated to cause vasodilation in numerous vascular beds that is mediated by V_2 , V_3 , 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 $\mu\text{U}/\text{kg}/\text{min}$. 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.

NDC 0517-1030-01: A carton of one multiple-dose vial containing vasopressin 10 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) Do not store above 25°C (77°F)	Opened (After First Puncture)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A
10 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days



AMERICAN REGENT, INC.
SHIRLEY, NY 11967

RQ1093-C

Rev. 1/2023

PRINCIPAL DISPLAY PANEL - Container Label (1 mL)

NDC 0517-1020-01

Rx Only

Vasopressin Injection, USP

20 Units per mL

For Intravenous Infusion
Must be diluted prior to use

1 mL Single-Dose Vial -
Discard Unused Portion

NDC 0517-1020-01 Rx Only

Vasopressin

Injection, USP

20 Units per mL

For Intravenous Infusion
Must be diluted prior to use

1 mL Single Dose Vial -
Discard Unused Portion

Contains 5 mg/mL
chlorobutanol as a
preservative.

Store refrigerated 2°C
to 8°C (36°F to 46°F).

Recommended
dosage: see prescribing
information.

RN1125-B

Rev. 1/2022

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01 103 0517 1020 01 5

PRINCIPAL DISPLAY PANEL - Carton Labeling (1 mL)

NDC 0517-1020-25

Vasopressin Injection, USP

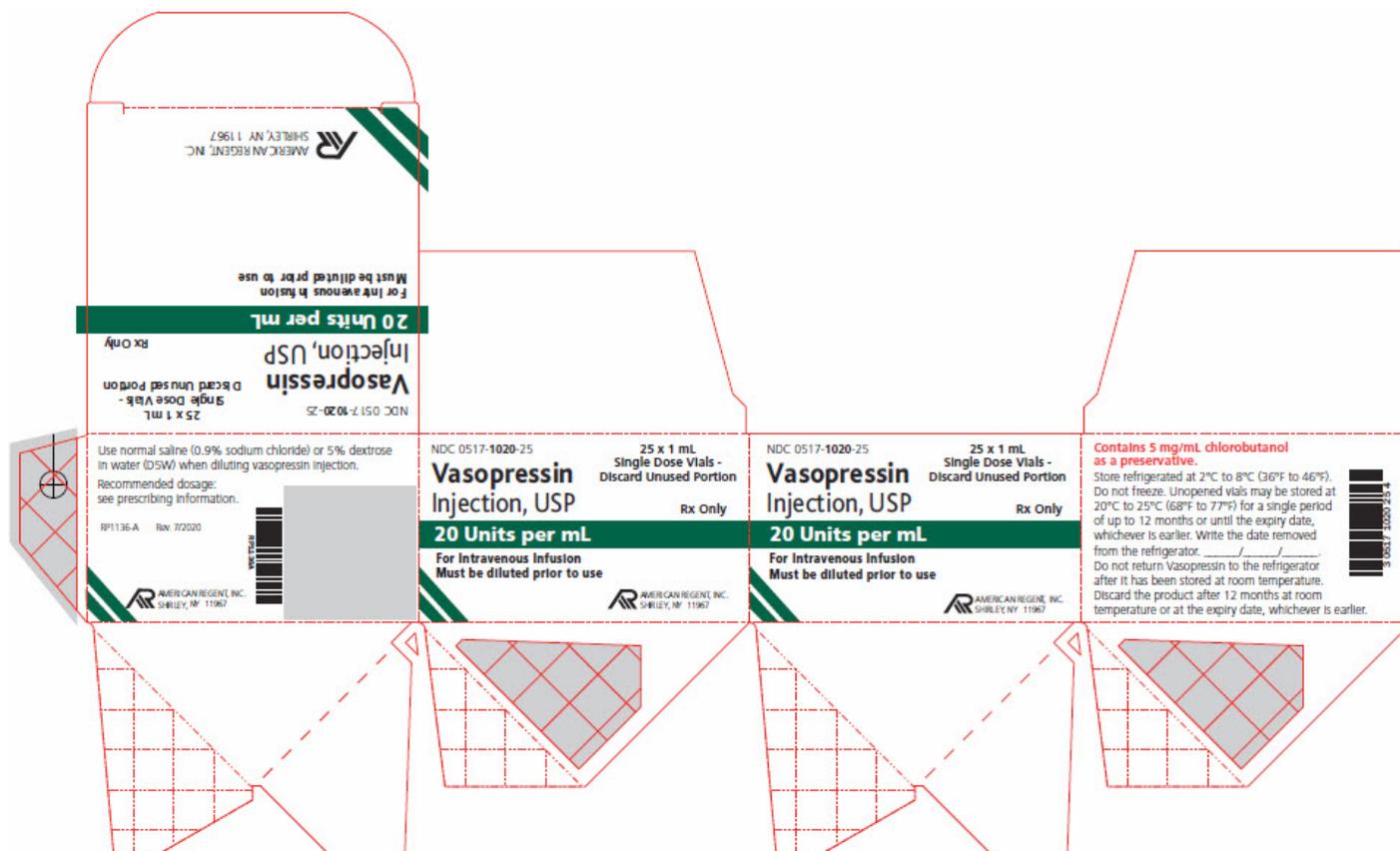
20 Units per mL

For Intravenous Infusion
Must be diluted prior to use

25 x 1 mL Single Dose Vials
Discard Unused Portion

Rx Only

AMERICAN REGENT, INC.
SHIRLEY, NY 11967



Serialization Label (1 mL)



LOT 0000
EXP 01/2099
GTIN 00305171020254
SN 1000000000001

PRINCIPAL DISPLAY PANEL - Container Label (10 mL)

NDC 0517-1030-01

Rx Only

Vasopressin Injection, USP

200 Units per mL 10 mL

(20 Units per mL)

For Intravenous Infusion.
Must be diluted prior to use.

10 mL Multiple-Dose Vial

NDC 0517-1030-01 Rx Only

Vasopressin
Injection, USP

200 Units per 10 mL
(20 Units per mL)

**For Intravenous Infusion.
Must be diluted prior to
use.**

10 mL Multiple-Dose Vial

Store between 2°C and 8°C (36°F and 46°F). Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months. Avoid Freezing.

Dosage: See full prescribing information.

After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days.

Discard after ____/____/____



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RN1178-B
Rev. 12/2022



(01)10305171030014

PRINCIPAL DISPLAY PANEL - Carton Labeling (10 mL)

NDC 0517-1030-01

Rx Only

Vasopressin Injection, USP

200 Units per 10 mL
(20 units per mL)

For Intravenous Infusion.
Must be diluted prior to use.

Store between 2°C and 8°C (36°F and 46°F).

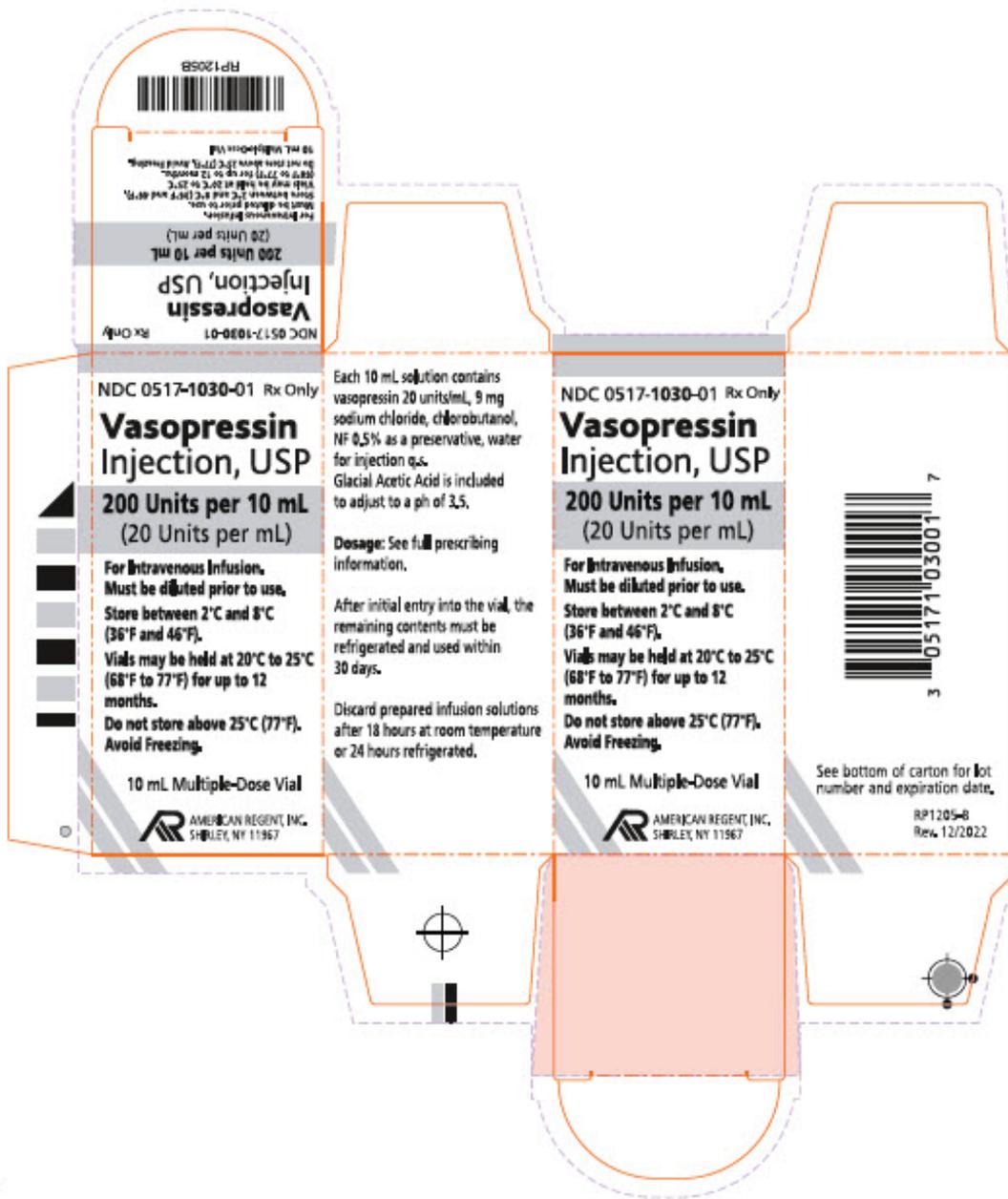
Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months.

Do not store above 25°C (77°F).

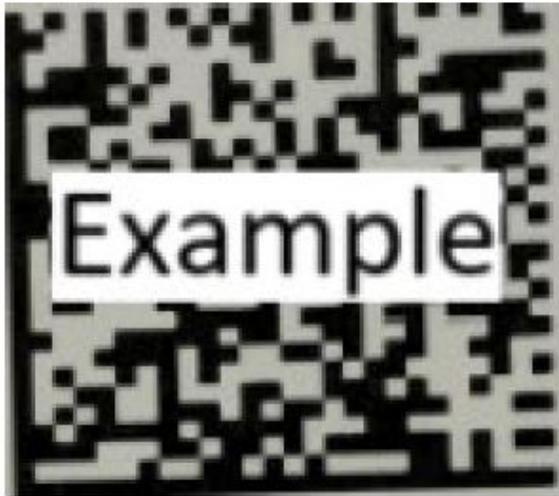
Avoid Freezing.

10 mL Multiple-Dose Vial

AMERICAN REGENT, INC.
SHIRLEY, NY 11967



Serialization Label (10 mL)



LOT XXXXXX

EXP MM/YYYY

GTIN 00305171030017

SN XXXXXXXXXXXXX

VASOPRESSIN

vasopressin injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0517-1020
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VASOPRESSIN (UNII: Y4907O6MFD) (VASOPRESSIN - UNII:Y4907O6MFD)	VASOPRESSIN	20 [USP'U] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	
ACETIC ACID (UNII: Q40Q9N063P)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	9 mg in 1 mL
CHLOROBUTANOL (UNII: HM4YQM8WRC)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0517-1020-25	25 in 1 CARTON	02/03/2022	
1	NDC:0517-1020-01	1 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212593	02/03/2022	

VASOPRESSIN

vasopressin injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0517-1030
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VASOPRESSIN (UNII: Y4907O6MFD) (VASOPRESSIN - UNII:Y4907O6MFD)	VASOPRESSIN	20 [USP'U] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	9 mg in 1 mL
ACETIC ACID (UNII: Q40Q9N063P)	
WATER (UNII: 059QF0KO0R)	
CHLOROBUTANOL (UNII: HM4YQM8WRC)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0517-1030-01	1 in 1 CARTON	06/21/2023	
1		10 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
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NDA	NDA212593	06/21/2023	
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Labeler - American Regent, Inc. (002033710)

Establishment

Name	Address	ID/FEI	Business Operations
American Regent, Inc.		606821721	manufacture(0517-1020, 0517-1030)

Revised: 1/2023

American Regent, Inc.