

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217569Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VASOPRESSIN IN SODIUM CHLORIDE INJECTION, for intravenous use

Initial U.S. Approval: 2014

-----INDICATIONS AND USAGE-----

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

-----DOSAGE AND ADMINISTRATION-----

- Post-cardiotomy shock: 0.03 units/minute to 0.1 units/minute by intravenous infusion. (2.1)
- Septic shock: 0.01 units/minute to 0.07 units/minute by intravenous infusion. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Injection: 100-mL single dose, ready-to-use containers with (3)

- 20 units vasopressin (0.2 units/mL) in 0.9% sodium chloride.
- 40 units vasopressin (0.4 units/mL) in 0.9% sodium chloride.

-----CONTRAINDICATIONS-----

- Vasopressin in Sodium Chloride Injection is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin. (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 **Baxter Healthcare** at 1-866-888-2472 or **FDA** at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Pressor effects of catecholamines and Vasopressin in Sodium Chloride Injection are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasopressin in Sodium Chloride 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 not been identified in older patients. (8.5)

Revised: 09/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasopressin in Sodium Chloride 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 Administration

This product does not require dilution prior to 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 by intravenous infusion

Septic Shock: 0.01 units/minute by intravenous infusion

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.

Inspect visually for any particulate matter and discoloration prior to administration.

Discard Unused Portion

Do not add supplemental medication or additive

3 DOSAGE FORMS AND STRENGTHS

Injection: a clear, practically colorless solution for intravenous infusion, supplied in 100-mL single dose ready-to-use containers as:

- 20 units vasopressin (0.2 units/mL) in 0.9% sodium chloride
- 40 units vasopressin (0.4 units/mL) in 0.9% sodium chloride

4 CONTRAINDICATIONS

Vasopressin in Sodium Chloride Injection is contraindicated in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

A decrease in cardiac index may be observed with the 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 reliably their frequency or 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 in Sodium Chloride 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 in Sodium Chloride 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

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 in Sodium Chloride 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 in Sodium Chloride 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 in Sodium Chloride 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.

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 in Sodium Chloride Injection may need to be increased [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

Maternal Adverse Reactions: Vasopressin in Sodium Chloride Injection may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.2 Lactation

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 in Sodium Chloride 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), *Adverse Reactions* (6), and *Clinical Pharmacology* (12.3)].

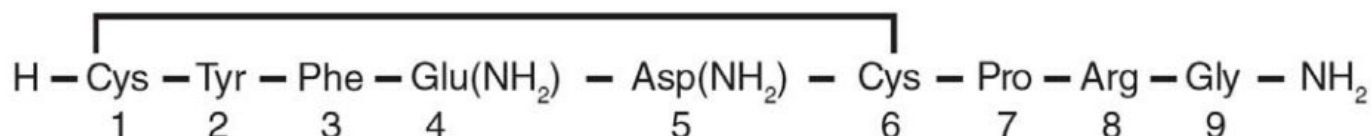
10 OVERDOSAGE

Overdosage with Vasopressin in Sodium Chloride 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 in Sodium Chloride Injection contains vasopressin, a polypeptide hormone. 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: $\text{C}_{46}\text{H}_{65}\text{N}_{15}\text{O}_{12}\text{S}_2$

Molecular Weight: 1084.23

Vasopressin in Sodium Chloride Injection is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. Each 100 mL contains 20 units (0.2 units/mL) or 40 units (0.4 units/mL) of vasopressin. Each 100mL also contains 900 mg Sodium Chloride, 33.6 mg Sodium DL-Lactate, and Water for Injection. pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. It has a pH of 3.6 – 4.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vasopressin causes vasoconstriction by binding to V_1 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 V_2 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 and ACTH 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 are 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 $\mu\text{U/kg/min}$. 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 Interaction Studies

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, alfentanyl and sufentanyl 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 function and fertilizing ability of spermatozoa.

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 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasopressin in Sodium Chloride Injection is supplied as a clear, practically colorless solution for intravenous administration in single-dose 100 mL ready-to-use containers available as:

Product Code	Product Description	NDC Number
2G3498	20 units vasopressin (0.2 units/mL) Supplied as 12 bags per carton	0338-9640-12
2G3499	40 units vasopressin (0.4 units/mL) Supplied as 12 bags per carton	0338-9647-12

Store in the refrigerator (2°C to 8°C [36°F to 46°F]). Protect from freezing.

Use within 72 hours once taken out of refrigerated condition.

The drug product must be stored in its light protective carton during storage.

Manufactured by, Packed by, Distributed by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Printed in USA

07-19-04-793

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Vasopressin

in 0.9% Sodium Chloride Injection

For Intravenous Infusion Only	Rx only
100 mL Single-Dose Container	Sterile
Discard Unused Portion	

Do not add supplemental medication or additives.

Code 2G3498
Product of USA
07-34-00-1681

NDC 0338-9647-12

Vasopressin

in 0.9% Sodium Chloride Injection

40 units per 100 mL (0.4 units/mL)

For Intravenous Infusion Only

Rx only

100 mL Single-Dose Container

Sterile

Discard Unused Portion

Each mL of the 0.4 units/mL strength also contains 9 mg sodium chloride, 0.336 mg sodium DL-lactate, and water for injection. pH may have been adjusted with sodium hydroxide or hydrochloric acid.

Dosage: See prescribing information.

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

Use within 72 hours once taken out of the refrigerated condition.

Protect from light. Protect from freezing.

Do not add supplemental medication or additives.

Baxter

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

Code 2G3499

Product of USA
07-34-00-1682

Reference ID: 5253461

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

Use within 72 hours once taken out of the refrigerated condition.

The drug product must be stored in its light protective carton during storage. Protect from freezing.

Do not add supplemental medication or additives.

Vasopressin
in 0.9% Sodium Chloride Injection

20 units per 100 mL (0.2 units/mL)

Contains: 6 x 100 mL Single-Dose bags.
Each bag contains 100 mL.

Baxter Rx only

*FOR BAR CODE POSITION ONLY	(01) 00000000000000	(10)XX000000
	(21) 00000000000000	(17)00000000

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

Use within 72 hours once taken out of the refrigerated condition.

The drug product must be stored in its light protective carton during storage. Protect from freezing.

Do not add supplemental medication or additives.

Vasopressin
in 0.9% Sodium Chloride Injection

20 units per 100 mL (0.2 units/mL)

Contains: 6 x 100 mL Single-Dose bags.
Each bag contains 100 mL.

Baxter Rx only

*FOR BAR CODE POSITION ONLY	(01) 00000000000000	(10)XX000000
	(21) 00000000000000	(17)00000000

NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXXX

For Intravenous Infusion only

Each mL of the 0.2 units/mL strength also contains 9 mg sodium chloride, 0.336 mg sodium DL-lactate, and water for injection. pH may have been adjusted with sodium hydroxide or hydrochloric acid.

Dosage: See prescribing information.

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

07-04-00-0841

NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXXX

For Intravenous Infusion only

Each mL of the 0.2 units/mL strength also contains 9 mg sodium chloride, 0.336 mg sodium DL-lactate, and water for injection. pH may have been adjusted with sodium hydroxide or hydrochloric acid.

Dosage: See prescribing information.

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

07-04-00-0841

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

Use within 72 hours once taken out of the refrigerated condition.

The drug product must be stored in its light protective carton during storage. Protect from freezing.

Do not add supplemental medication or additives.

Vasopressin

in 0.9% Sodium Chloride Injection

40 units per 100 mL (0.4 units/mL)

Contains: 6 x 100 mL Single-Dose bags.
Each bag contains 100 mL.

Baxter Rx only

*FOR BAR CODE POSITION ONLY	(01) 00000000000000	(10)XX000000
	(21) 000000000000	(17)00000000

NDC 0338-9647-12
Code 2G3499

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXXX

For Intravenous Infusion only

Each mL of the 0.4 units/mL strength also contains 9 mg sodium chloride, 0.336 mg sodium DL-lactate, and water for injection. pH may have been adjusted with sodium hydroxide or hydrochloric acid.

Dosage: See prescribing information.

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07-04-00-0842

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

Use within 72 hours once taken out of the refrigerated condition.

The drug product must be stored in its light protective carton during storage. Protect from freezing.

Do not add supplemental medication or additives.

Vasopressin

in 0.9% Sodium Chloride Injection

40 units per 100 mL (0.4 units/mL)

Contains: 6 x 100 mL Single-Dose bags.
Each bag contains 100 mL.

Baxter Rx only

*FOR BAR CODE POSITION ONLY	(01) 00000000000000	(10)XX000000
	(21) 000000000000	(17)00000000

NDC 0338-9647-12
Code 2G3499

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXXX

For Intravenous Infusion only

Each mL of the 0.4 units/mL strength also contains 9 mg sodium chloride, 0.336 mg sodium DL-lactate, and water for injection. pH may have been adjusted with sodium hydroxide or hydrochloric acid.

Dosage: See prescribing information.

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

07-04-00-0842

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/s/

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