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27 August 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir or Madam:

The undersigned submits this petition, pursuant to Section 505(j)(2)(C) of the Federal Food Drug, and Cosmetic Ac, and in accordance with 21 CFR 314.93, 21 CFR 10.20, and 21 CFR 10.30 requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Vasopressin in 0.9% Sodium Chloride Injection 50 units per 50 mL (1 unit/mL) is suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that Vasopressin in 0.9% Sodium Chloride Injection, 50 unit/50 mL (1 unit/mL) in a single dose ready-to-use container is suitable for submission as an ANDA.

The reference listed drug product (RLD), upon which this petition is based is Vasopressin in 0.9% Sodium Chloride Injection, 20 unit/100 mL (0.2 units/mL) and 40 units/100 mL (0.4 unit/mL) by Baxter Healthcare Corporation NDA # 217569 (approved 29 September 2023). Therefore, the petitioner seeks a change in strength from 20 units/100 mL (0.2 mg/mL) and 40 units/100 mL (0.4 mg/mL) to 50 unit/50 mL (1 mg/mL) single dose in a ready-to-use container.

FRESENIUS KABI

B. Statement of Grounds

Under 21 U.S.C. § 355(j)(2)(C), a petition may be filed with the Agency seeking permission to file an ANDA for a proposed drug product that differs from the RLD in "strength".

The RLD, Vasopressin in 0.9% Sodium Chloride Injection by Baxter Healthcare Corporation is an intravenous infusion product containing Vasopressin (20 units/100 mL and 40 units/100 mL). It does not require dilution prior to administration. The FDA approved NDA # 217569 on 29 September 2023. Please refer to listing in the current electronic edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (**Attachment 1**).

The active ingredient in the proposed product is identical to that of the RLD and hence as required by 21 CFR 314.93(d)(1) and (2), is of the same pharmacological and therapeutic class and can be expected to have the same therapeutic effect as the RLD when administered to patients for the conditions of use in the RLD's Prescribing Information (PI) (**Attachment 2**).

This petition is seeking a change in strength (total drug content and volume) from the RLD's 20 unit/100 mL (0.2 units/mL) and 40 units/100 mL (0.4 unit/mL) in a single dose ready-to-use container to the proposed 50 unit/50 mL (1 unit/mL) in a single dose ready-to-use container.

The proposed change in strength would fulfil dosages already provided for in the approved RLD labeling. Changes in the labeling would be limited to describing the proposed new presentation sought in this petition. The uses, indications, warnings and directions for use will remain the same as that of the RLD. Draft labeling for the proposed product is included in **Attachment 3**.

The additional proposed strength compared to the two strengths approved in the RLD would allow for addressing the approved higher dosing recommendations with fewer number of iv bags. For example, according to the Dosage and Administration Section in the RLD's current approved PI for Vasopressin in 0.9% Sodium Chloride Injection the maximum dosage of an individual for post-cardiotomy shock is up to 0.1 unit/minute. If Vasopressin is to be administered for a full day (60 min X 24 hrs = 1,440 minutes) in these patients, then a total of 144 units of Vasopressin would need to be administered. Listed below in Table 1 is the calculated number of bags for each strength that will need to be used to address this dosing requirement. When the maximum total dose as per the approved PI is required, a larger number of bags with the lower strengths as approved for the RLD are required, namely a total of ~8 bags and ~4 bags for 20 units/100 mL and 40 units/100 mL, respectively.

The proposed 50 unit/50 mL (1 unit/mL) presentation more closely matches the maximum dose range of Vasopressin in Sodium Chloride Injection and will only require ~ 3 bags. This will result in fewer iv bag changes per day with minimal wastage of the drug when dosed according to the approved RLD labeling.

Table 1. Comparison of Drug Product to be Administered with Proposed and Currently Approved Presentations

Maximum Daily Dosage	Approved Presentations (RLD)		Proposed Drug Product (Fresenius Kabi)	
	Strength	**Number of bags**	**Strength**	**Number of bags**
144 units/day (0.1 unit/min x 60 min x 24 hours)	20 unit/100 mL (0.2 unit/mL)	7.2 bags	50 unit/50 mL (1 unit/mL)	2.9 bags
	40 unit/100 mL (0.4 unit/mL)	3.6 bags		

Furthermore, the proposed 1 unit/mL strength can be used in patients that have fluid restrictions as noted in the dosage instructions for the concentrated single dose vials for Vasopressin Injection (***Vasostrict® NDA 204485, PI April 2023***). Instructions are provided to the healthcare provider to dilute the concentrated Vasopressin Injection (20 units/mL) to a 1 unit/mL strength by diluting with either 0.9% Sodium Chloride or 5% Dextrose with this strength being used if fluid restriction is necessary.

The sponsor's proposed formulation at this 1 unit/mL strength will eliminate the need for this dilution step and provide a strength that will be dosed as per the approved RLD's PI for patients that need fluid restriction.

The American Society of Health-System Pharmacists' (ASHP) has published adult continuous infusion standards as part of the Standardize 4 Safety Initiative to standardize medication concentrations to reduce errors, especially during transitions of care (***ASHP June 2024***). As per these Standards more concentrated IV solutions are recommended to be used when appropriate based on the patient's clinical need related to their fluid status. Additionally, as per these Standards, ASHP has published recommended standard concentrations to be used and Vasopressin 1 unit/mL concentration is included as a third recommended concentration together with the RLD's approved 0.2 unit/mL and 0.4 unit/mL concentrations. The additional strength proposed by Fresenius Kabi in this petition will provide the added benefit of including this standardized concentration for use in patients that require this dosing as per the approved PI.

As stated above, there are no proposed changes to the dosing in labeling with the only changes being the obvious addition in strength sought in this petition. Draft labeling for the proposed product is included in Attachment 3, and the RLD's approved labeling is provided in Attachment 2.

Therefore, the petitioner's request to the Commissioner for a change in strength (i.e., a change in total drug content from 20 unit/100 mL and 40 unit/100 mL to 50 unit/50 mL) for Vasopressin in 0.9% Sodium Chloride Injection should raise no additional safety or effectiveness questions and

can be adequately evaluated in an ANDA without additional data from investigations to establish safety or effectiveness of the proposed change.

Fresenius Kabi acknowledges that as per 21 CFR 314.93(e)(1)(vi), a petition under 505(j)(2)(C), may be denied if there is "[a] drug product…approved in an NDA for the change described in the petition." Although, at the time of this petition's submission there are two NDAs for Vasopressin approved with a concentration of 1 unit/mL, Fresenius Kabi maintains that these formulations are not applicable to the proposed product that is the subject of this petition referencing Baxter's NDA 217569.

The two approved products are Vasopressin in Sodium Chloride Injection (NDA # 217766) held by Long Grove Pharms and Vasostrict® (NDA # 204485) held by Endo Operations. Fresenius Kabi's proposed formulation and the RLD proposed for the ANDA does not contain the same inactive ingredients as these approved products and these two other drug products at the 1 unit/mL strength cannot be considered as and are not listed as being therapeutically equivalent. Long Grove's Vasopressin in Sodium Chloride Injection (NDA 217766) formulation utilizes different excipients (aspartic acid and boric acid) as well as chlorobutanol which are not contained in the petitioner's formulation that is equivalent to the Baxter RLD (***Vasopressin in Sodium Chloride NDA 217766, PI July 2024***). As per 21 CFR 314.94(a)(9)(iii), pH adjusters are not one of the categories (preservative, buffer, or antioxidant) that an applicant's formulation can differ from the reference listed drug. The other NDA, Vasostrict® (Vasopressin) (NDA # 204485) held by Endo Operations, also contains a different formulation. The petitioner's formulation utilizes sodium chloride as a tonicity adjuster while Vasostrict® is in a dextrose solution. Since both these alternate approved applications utilize different formulations than the proposed formulation, the petitioner cannot reference NDA 217766 or NDA 204485 as the Reference Listed Drug in its application.

C. Inapplicability of the Pediatric Research Equity Act (PREA)

The Pediatric Research Equity Act (PREA) requires certain applications for a drug to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. PREA applies to all applications for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. PREA does not apply to applications containing a new strength such as the one proposed in this petition.

D. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31 and an environmental assessment is not required.

E. Economic Impact

The petitioner does not believe that this is applicable in this case but will agree to provide such an analysis if requested by the Agency.

F. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

John McNally

Digitally signed by John McNally
DN: c=US, serialNumber=MAS20240418467586, st=Illinois, l=Lake Zurich, o=Fresenius Netcare, ou=IT, cn=John McNally, email=john.mcnally@fresenius-kabi.com
Date: 2024.08.27 16:42:14 -05'00'

John McNally
Three Corporate Drive
Lake Zurich, IL 60047
847-550-2013

Attachments:

1. Vasopressin in 0.9% Sodium Chloride Injection, NDA 217569, product information from the current edition of the electronic Approved Drug Products with Therapeutic Equivalence Evaluations
2. Approved Prescribing Information for Vasopressin in 0.9% Sodium Chloride Injection, Baxter Healthcare Corporation, NDA 217569, February 2024.
3. Fresenius Kabi USA's Draft Prescribing Information for Vasopressin in 0.9% Sodium Chloride Injection
4. References
    i. *Approved Prescribing Information, Vasostrict®, NDA 204485, April 2023*
    ii. *ASHP Standard 4 Safety Initiative: Adult Continuous Infusion Standards*
    iii. *Approved Prescribing Information, Vasopressin in Sodium Chloride Injection, NDA 217766, July 2024*

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	VASOPRESSIN	VASOPRESSIN IN SODIUM CHLORIDE 0.9%	N217569	SOLUTION	INTRAVENOUS	20UNITS/100ML (0.2UNITS/ML)		RLD	RS	BAXTER HEALTHCARE CORP
RX	VASOPRESSIN	VASOPRESSIN IN SODIUM CHLORIDE 0.9%	N217569	SOLUTION	INTRAVENOUS	40UNITS/100ML (0.4UNITS/ML)		RLD	RS	BAXTER HEALTHCARE CORP

VASOPRESSIN IN 0.9% SODIUM CHLORIDE- vasopressin in 0.9% sodium chloride injection
Baxter Healthcare Corporation

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 antiduretic 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: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

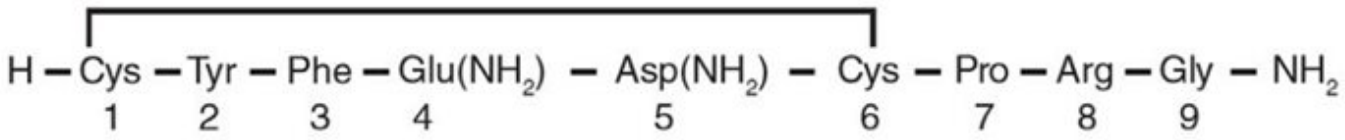
Overdosage with Vasopressin in Sodium Chloride Injection can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to

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: $C_{46}H_{65}N_{15}O_{12}S_2$ 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 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 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 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 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.

If needed, Vasopressin in Sodium Chloride Injection may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature or until the expiration date printed on the carton and container label, whichever is earlier. Once stored at room temperature, do not place back in the refrigerator.

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

07-19-06-884

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 0338-9640-12

Vasopressin

in 0.9% Sodium Chloride Injection

20 units per 100 mL (0.2 units/mL)

For Intravenous Infusion Only Rx only

100 mL Single-Dose Container Sterile

Discard Unused Portion

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.

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.

Protect from light. Protect from freezing.

Do not add supplemental medication or additives.

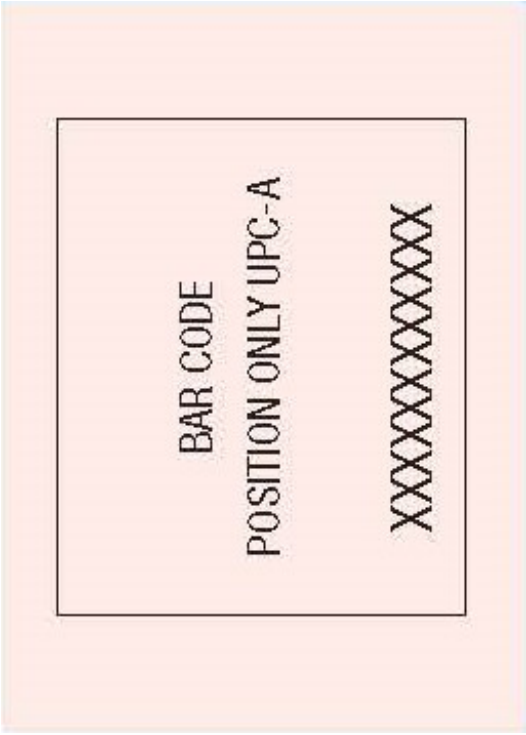
Code 2G3498

Baxter

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

Product of USA

07-34-00-2001



Container Label

NDC 0338-9640-12

Vasopressin
in 0.9% Sodium Chloride Injection
20 units per 100 mL (0.2 units/mL)

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

Rx only
Sterile

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.

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.

Protect from light. Protect from freezing.

Do not add supplemental medication or additives.

Code 2G3498

BaxterLogo
Baxter Healthcare Corporation, Deerfield, IL 60015 USA

Product of USA
07-34-00-2001

BAR CODE
POSITION ONLY UPCA-A

XXXXXXXXXXXX

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]).

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.

Protect from light. Protect from freezing.

Do not add supplemental medication or additives.

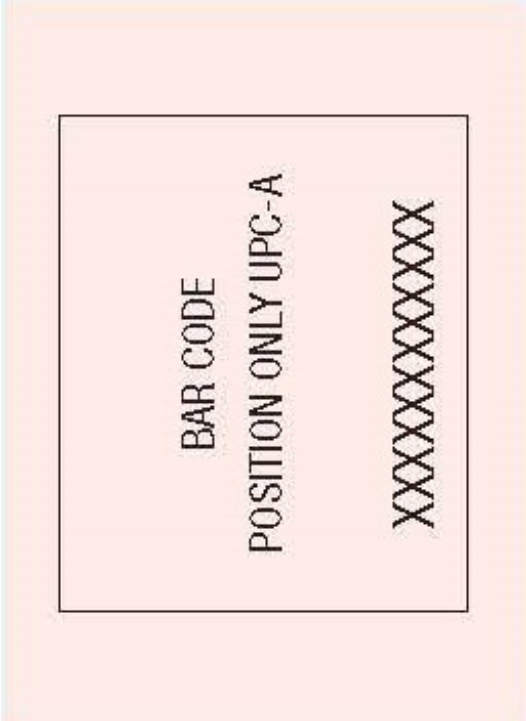
Code 2G3499

Baxter

Baxter Healthcare Corporation, Deerfield, IL 60015 USA

Product of USA

07-34-00-2002



Container Label

NDC 0338-9647-12

Vasopressin
in 0.9% Sodium Chloride Injection
40 units per 100 mL (0.4 units/mL)

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

Rx only
Sterile

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]).

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.

Protect from light. Protect from freezing.

Do not add supplemental medication or additives.

Code 2G3499

Baxter Logo
Baxter Healthcare Corporation, Deerfield, IL 60015 USA

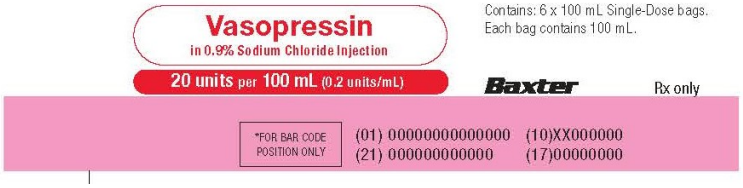
Product of USA
07-34-00-2002

BAR CODE
POSITION ONLY UPCA-A

XXXXXXXXXXXX

Store refrigerated (2°C to 8°C [36°F to 46°F]).
If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.
The drug product must be stored in its light protective carton during storage.
Protect from freezing.
Do not add supplemental medication or additives.

Store refrigerated (2°C to 8°C [36°F to 46°F]).
If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.
The drug product must be stored in its light protective carton during storage.
Protect from freezing.
Do not add supplemental medication or additives.



NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXX

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

07-04-00-1121

NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXX

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

07-04-00-1121

Carton Label

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.

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.

BaxterLogo

Rx only

*FOR BAR CODE POSITION ONLY

(01) 00000000000000
(10)XX000000
(21) 000000000000
(17)00000000

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.

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.

BaxterLogo

Rx only

*FOR BAR CODE POSITION ONLY

(01) 00000000000000
(10)XX000000
(21) 000000000000
(17)00000000

NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXX

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 and/or hydrochloric acid.
Dosage: See prescribing information.

Baxter Healthcare Corporation,Deerfield, IL 60015 USA

07-04-00-1121

NDC 0338-9640-12
Code 2G3498

*FOR BAR CODE POSITION ONLY

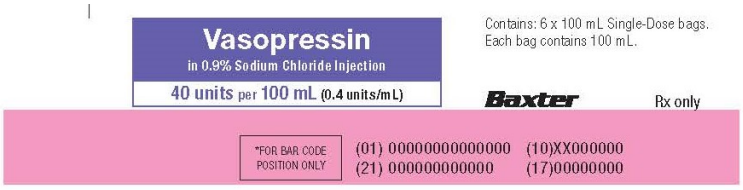
(01) XXXXXXXXXXXXXX

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 and/or hydrochloric acid.
Dosage: See prescribing information.

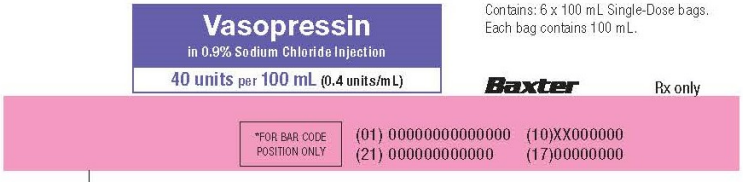
Baxter Healthcare Corporation,Deerfield, IL 60015 USA

07-04-00-1121

Store refrigerated (2°C to 8°C [36°F to 46°F]).
If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.
The drug product must be stored in its light protective carton during storage.
Protect from freezing.
Do not add supplemental medication or additives.



Store refrigerated (2°C to 8°C [36°F to 46°F]).
If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months. Discard after 6 months if stored at room temperature.
The drug product must be stored in its light protective carton during storage.
Protect from freezing.
Do not add supplemental medication or additives.



Carton Label

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.

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.

BaxterLogo

Rx only

*FOR BAR CODE POSITION ONLY

(01) 00000000000000
(10)XX000000
(21) 000000000000
(17)00000000

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

If needed, product may be stored at room temperature up to 25°C (77°F) for up to 6 months.
Discard after 6 months if stored at room temperature.

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.

BaxterLogo

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) XXXXXXXXXXXXXX

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 and/or hydrochloric acid.
Dosage: See prescribing information.

Baxter Healthcare Corporation,Deerfield, IL 60015 USA

07-04-00-1122

NDC 0338-9647-12
Code 2G3499

*FOR BAR CODE POSITION ONLY

(01) XXXXXXXXXXXXXX

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 and/or hydrochloric acid.
Dosage: See prescribing information.

Baxter Healthcare Corporation,Deerfield, IL 60015 USA

07-04-00-1122

VASOPRESSIN IN 0.9% SODIUM CHLORIDE

vasopressin in 0.9% sodium chloride injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0338-9640
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 100 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	900 mg in 100 mL
SODIUM LACTATE (UNII: TU7HW0W0QT)	33.6 mg in 100 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0338-9640-12	12 in 1 CARTON	09/29/2023	
1		100 mL in 1 BAG; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217569	09/29/2023	

VASOPRESSIN IN 0.9% SODIUM CHLORIDE

vasopressin in 0.9% sodium chloride injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0338-9647
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VASOPRESSIN (UNII: Y4907O6MFD) (VASOPRESSIN - UNII:Y4907O6MFD)	VASOPRESSIN	40 [USP'U] in 100 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	900 mg in 100 mL
SODIUM LACTATE (UNII: TU7HW0W0QT)	33.6 mg in 100 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0338-9647-12	12 in 1 CARTON	09/29/2023	
1		100 mL in 1 BAG; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217569	09/29/2023	

Labeler - Baxter Healthcare Corporation (005083209)

Establishment

Name	Address	ID/FEI	Business Operations
Baxter Healthcare Corporation		194684502	ANALYSIS(0338-9640, 0338-9647)

Revised: 2/2024 Baxter Healthcare Corporation

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 to 0.1 units/minute by intravenous infusion (2.1)
• Septic shock: 0.01 to 0.07 units/minute by intravenous infusion (2.1)
----------DOSAGE FORMS AND STRENGTHS----------
20 units vasopressin per 100 mL (0.2 units per mL) in 0.9% sodium chloride
40 units vasopressin per 100 mL (0.4 units per mL) in 0.9% sodium chloride
50 units vasopressin per 50 mL (1 unit per mL) in 0.9% sodium chloride
----------CONTRAINDICATIONS----------
• Vasopressin in Sodium Chloride Injection is contraindicated in patients with a 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 Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
----------DRUG INTERACTIONS----------
• Pressor effects of catecholamines and Vasopressin is 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 antiduretic 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 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: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

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

- 20 units vasopressin (0.2 units per mL) in 100 mL of 0.9% sodium chloride
- 40 units vasopressin (0.4 units per mL) in 100 mL of 0.9% sodium chloride
- 50 units vasopressin (1 unit per mL) in 50 mL of 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 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 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 (2.2) 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)]*.

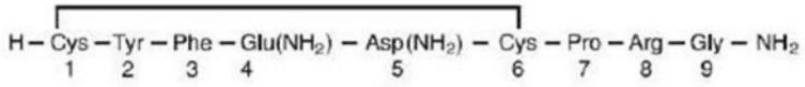
10 OVERDOSAGE

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: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

Vasopressin in Sodium Chloride Injection is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. Each mL contains either 0.2 units, 0.4 units, or 1 unit of vasopressin. Each mL also contains 9 mg Sodium Chloride, 0.042 mg Glacial Acetic Acid, and 0.0136 mg of Sodium Acetate.

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/1 1-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 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 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 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 $\leq$ 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 a single-dose ready-to-use container available as:

Product Code	Unit of Sale	Strength	Unit of Use
XXXXX	NDC XXXXX 12 bags per carton	20 Units vasopressin per bag (0.2 units per mL)	NDC XXXXX 100 mL fill in a 100-mL bag
XXXXX	NDC XXXXX 12 bags per carton	40 Units vasopressin per bag (0.2 units per mL)	NDC XXXXX 100 mL fill in a 100-mL bag
XXXXX	NDC XXXXX 12 bags per carton	50 Units vasopressin per bag (1 unit per mL)	NDC XXXXX 50 mL fill in a 50-mL bag

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

If needed, Vasopressin in Sodium Chloride Injection may be stored at room temperature up to 25°C (77°F) for up to TO BE DETERMINED. Discard after TO BE DETERMINED if stored at room temperature or until the expiration date printed on the carton and container label, whichever is earlier. Once stored at room temperature, do not place back in the refrigerator. The drug product must be stored in its light protective overwrap during storage.

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