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

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.

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 t½ of vasopressin at these levels is ≤10 minutes.

Excretion

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

6.0 NON-CLINICAL PHARMACOLOGY

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.

Water intoxication may be treated with water restriction and temporary withdrawal of Vasopressin until polyuria occurs. Severe water intoxication may require osmotic diuresis with mannitol, hypertonic dextrose, or urea alone or with furosemide.

7.0 PHARMACEUTICAL PARTICULARS

7.1 Presentation

CPRESSIN™ - A pack containing 1 pre-filled syringe of 1 ml

CPRESSIN-P™ - A pack containing 5 ampoules of 1 ml

7.2 Storage

Store below 25°C. Do not freeze.
Keep out of reach of children

Manufactured by:

SAMARTH LIFE SCIENCES PVT. LTD.

Nangal Uperla, Swarghat Road, Nalagarh, Dist. Solan,
Himachal Pradesh - 174101, India.
H.O.: Ram Mandir Road, Goregaon (W),
Mumbai - 400 104, India.

™ Trade Mark of Samarth

10415-2

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞

Vasopressin Injection IP

CPRESSIN™ / CPRESSIN-P™

For IV/IM/SC use only

1. NAME OF THE MEDICINAL PRODUCT

CPRESSIN™ (Vasopressin Injection IP 40 units / 1 ml)

CPRESSIN-P™ (Vasopressin Injection IP 20 units / 1 ml)

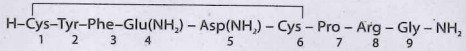
2. COMPOSITION

CPRESSIN™
Each prefilled syringe contains:
Vasopressin IP.....40 units
(Synthetic)
Water for Injections IP.....q.s.

CPRESSIN-P™
Each ml contains:
Vasopressin IP.....20 units
(Synthetic)
Water for Injections IP.....q.s.

3. DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis.
The chemical name of Vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-LGlutaminyl-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

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- To increase blood pressure in adults with vasodilatory shock (e.g., postcardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
- For prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.

4.2 Dosage and Administration

- **To increase blood pressure in adults with vasodilatory shock (e.g., postcardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.**

Preparation of Diluted Solutions

Dilute Vasopressin in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. 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	Diluent
No	0.1 units/ml	2.5 ml(50 units)	500 ml
Yes	1 unit/ml	5 ml(100 units)	100 ml

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

Administration

In general, titrate to the lowest dose compatible with a clinically acceptable response.
Post-cardiotomy shock: start with a dose of 0.03 units/minute.
Septic shock: start with a dose of 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 by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

- **For prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas**

shadows, and in diabetes insipidus.

Ten units of Vasopressin (0.5 ml) will usually elicit full physiologic response in adult patients; 5 units will be adequate in many cases. Vasopressin should be given intramuscularly at 3- or 4-hour intervals as needed. The dosage should be proportionately reduced for pediatric patients.
When determining the dose of Vasopressin for a given case, the following should be kept in mind.
It is particularly desirable to give a dose not much larger than is just sufficient to elicit the desired physiologic response. Excessive doses may cause undesirable side effects—blanching of the skin, abdominal cramps, nausea—which, though not serious, may be alarming to the patient. Spontaneous recovery from such side effects occurs in a few minutes. It has been found that one or two glasses of water given at the time Vasopressin is administered reduce such symptoms.
It is particularly desirable to give a dose not much larger than is just sufficient to elicit the desired physiologic response. Excessive doses may cause undesirable side effects—blanching of the skin, abdominal cramps, nausea—which, though not serious, may be alarming to the patient. Spontaneous recovery from such side effects occurs in a few minutes. It has been found that one or two glasses of water given at the time Vasopressin is administered reduce such symptoms.

Abdominal Distention
In the average postoperative adult patient, give 5 units (0.25 ml) initially; increase to 10 units (0.5 ml) at subsequent injections if necessary. It is recommended that Vasopressin be given intramuscularly and that injections be repeated at 3- or 4-hour intervals as required. Dosage to be reduced proportionately for pediatric patients.

Vasopressin used in this manner will frequently prevent or relieve postoperative distention. These recommendations apply also to distention complicating pneumonia or other acute toxemias.

Abdominal Roentgenography
For the average case, two injections of 10 units each (0.5 ml) are suggested. These should be given two hours and one-half hour, respectively, before films are exposed. Many roentgenologists advise giving an enema prior to the first dose of Vasopressin.

Diabetes Insipidus
Vasopressin may be given by injection. The dose by injection is 5 to 10 units (0.25 to 0.5 ml) repeated two or three times daily as needed.

Method of Administration
FOR IV/IM/SC USE

Conventionally Cpressin available in pfs should be administered by IM / SC route.
Cpressin-P available in ampoules should be administered by IV route.

4.3 Contraindications
Vasopressin is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine Vasopressin or Chlorobutanol.

4.4 Warnings and Precautions
Warnings
This drug should not be used in patients with vascular disease, especially disease of the coronary arteries, except with extreme caution. In such patients, even small doses may precipitate anginal pain, and with larger doses, the possibility of myocardial infarction should be considered.
Vasopressin may produce water intoxication. The early signs of drowsiness, listlessness, and headaches should be recognized to prevent terminal coma and convulsions.

Precautions
Worsening Cardiac Function
Use in patients with impaired cardiac response may worsen cardiac output.
General
Vasopressin should be used cautiously in the presence of epilepsy, migraine, asthma, heart failure, or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system.
Chronic nephritis with nitrogen retention contraindicates the use of Vasopressin until reasonable nitrogen blood levels have been attained.
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.

4.5 Drug Interactions
The following drugs may potentiate the antidiuretic effect of Vasopressin when used concurrently: carbamazepine; chlorpropamide; clofibrate; urea; fludrocortisone; tricyclic antidepressants. 2) The following drugs may decrease the antidiuretic effect of Vasopressin when used concurrently: demeclocycline; norepinephrine; lithium; heparin; alcohol. 3) Ganglionic blocking agents may produce a marked increase in sensitivity to the pressor effects of Vasopressin.
Catecholamines
Use with catecholamines is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.
Indomethacin
Use with indomethacin may prolong the effect of Vasopressin on cardiac index and systemic vascular resistance.
Ganglionic Blocking Agents
Use with ganglionic blocking agents may increase the effect of Vasopressin on mean arterial blood pressure.
Furosemide
Use with furosemide increases the effect of Vasopressin on osmolar clearance and urine flow.
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.

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.

4.6 Use in Specific Populations
Pregnancy
Risk Summary
There are no available data on Vasopressin 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 may need to be increased.
Maternal Adverse Reactions
Vasopressin may produce tonic uterine contractions that could threaten the continuation of pregnancy.

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.

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

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.

4.7 Adverse Reactions
Local or systemic allergic reactions may occur in hypersensitive individuals. The following side effects have been reported following the administration of Vasopressin.
Body as a Whole: anaphylaxis (cardiac arrest and/or shock) has been observed shortly after injection of Vasopressin.
Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding
Cardiac disorders: cardiac arrest, circumoral pallor, arrhythmias, decreased cardiac output, angina, myocardial ischemia, peripheral vasoconstriction, and gangrene, Right heart failure, atrial fibrillation, bradycardia
Gastrointestinal disorders: Mesenteric ischemia, abdominal cramps, nausea, vomiting, passage of gas.
Nervous System: tremor, vertigo, "pounding" in head.
Respiratory: bronchial constriction.
Hepatobiliary: Increased bilirubin levels
Renal/urinary disorders: Acute renal insufficiency
Vascular disorders: Distal limb ischemia
Metabolic: Hyponatremia
Skin: Sweating, urticaria, cutaneous gangrene, Ischemic lesions

4.8 Overdosage
Overdosage with Vasopressin 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.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacodynamics
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 adenyl cyclase.
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 gastrointestinaltract mediated by muscular V1-receptors and release of prolactin and ACTH via V3 receptors. At lower concentrations typical for the antidiuretic hormone Vasopressin inhibits water diuresis via renal V2 receptors. In patients with vasodilatory shock Vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous Vasopressin. Onset of the pressor effect of Vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of Vasopressin in patients.
The antidiuretic action of Vasopressin is ascribed to increasing reabsorption of water by the renal tubules.
Vasopressin can cause contraction of smooth muscle of the gastrointestinal tract and of all parts of the vascular bed, especially the capillaries, small arterioles, and venules with less effect on the smooth musculature of the large veins. The direct effect on the contractile elements is neither antagonized by adrenergic blocking agents nor prevented by vascular denervation.

5.2 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