SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

DOPA PLUS (Dopamine Hydrochloride 200mg/5ml Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40mg dopamine hydrochloride USP
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Liquid Injection

Colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dopamine Injection is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Patients most likely to respond adequately to Dopamine Injection are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and dopamine injection, the better the prognosis. Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of dopamine Injection.

Poor Perfusion of Vital Organs: Administration of Dopamine Injection in oliguric or anuric patients results in increase urine flow which. In some cases reached normal levels. Dopamine Injection may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of preexisting fluid accumulation. It should be noted that at doses above those optimal for the individual patient urine flow may decrease, necessitating reduction of dosage.

Low Cardiac Output: Increased cardiac output is related to the direct inotropic effect on the myocardium. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g., femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac

output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. The increase in cardiac output produced by dopamine is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension:

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of dopamine, which have little effect on SVR. At high therapeutic doses, the alpha adrenergic activity of dopamine becomes more prominent and thus may correct hypotension due to diminished SVR. in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration.

Therefore, it is suggested that the physician administer Dopamine Hydrochloride, USP as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

4.2 Posology and method of administration

WARNING: This is a potent drug: It must be diluted before administration to patient.

Dopamine hydrochloride Injection USP is administered (only after dilution) by intravenous infusion.

Suggested Dilution: Transfer contents of one or more ampoules or vials by aseptic technique to either 250 mL or 500 mL of one of the following sterile intravenous solutions just prior to administration:

1. Sodium Chloride Injection, USP
2. Dextrose (5%) Injection, USP
3. Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4. 5% Dextrose in 0.45% Sodium Chloride Solution
5. Dextrose (5%) in Lactated Ringer's Solution
6. Sodium Lactate (1/6 Molar) Injection, USP
7. Lactated Ringer's Injection, USP

The resultant dilutions are summarized in the following chart:

Concentration of Dopamine Hydrochloride	**40 mg/mL**	
Volume of Dopamine Hydrochloride Injection, USP	5 mL	10 mL
250 mL Bottle of I.V. Solution	800 mcg/mL	1600 mcg/mL
500 mL Bottle of I.V. Solution	400 mcg/mL	800 mcg/mL
1000 mL Bottle of I.V. Solution	200 mcg/mL	400 mcg/mL

Dopamine Hydrochloride Injection, USP has been found to be stable for a minimum of 24 hours after dilution in the foregoing intravenous solutions. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do NOT add Dopamine Hydrochloride to Sodium Bicarbonate Injection, USP or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration: Dopamine Hydrochloride Injection, USP after dilution, is administered intravenously through a suitable intravenous catheter or needle. When administering Dopamine Hydrochloride (or any potent medication) by continous intravenous infusion. It is advisable to use a problem volume control intravenous set. Each patient must be individually titrated to the desired hemodynamic or renal response to dopamine.

In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration rates greater than 50 mcg/kg/minute have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

4.3 Contraindications

Dopamine Injection should not be used in patients with pheochromocytoma. It should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

4.4 Special warnings and precautions for use

Warning:

Dopamine Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown, and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Do NOT add dopamine to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monoamine oxidase (MAO) inhibitors prior to the administration of dopamine will require substantially reduced dosage.

Precaution

General

1. Monitoring – Careful monitoring of the following indices is necessary during dopamine Injection infusion, as with any adrenergic agent, cardiac output, blood pressure, urine flow and when possible, cardiac output and pulmonary wedge pressure.

2. Hypovolemia - Prior to treatment with Dopamine Injection, hypovolemia should be fully corrected, if possible with either whole blood or plasma as indicated. Monitoring of central venous pressure of left ventricular filling pressure may be helpful in detecting and treating hypovolemia.

3. Hypoxia, Hypercapnia, Acidosis - These conditions which may also reduce the effectiveness and/or increase the incidence of adverse effects of dopamine, must be identified and corrected prior to, or concurrently with administration of dopamine Injection.

4. Decreased Pulse Pressure - If a disproportionate rise in the diastolic pressure (i.e., a marked decrease in the pulse pressure) is observed in patients receiving Dopamine Injection, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

5. Ventricular Arrhythmias - If an increased number of ectopic beats are observed, the dose should be reduced if possible.

6. Hypotension - At lower infusion rates, if hypotension occurs, the infusion rate should be rapidly increased until adequate blood pressure is obtained. If hypotension persists, dopamine HCl should be discontinued and a more potent vasoconstrictor agent such as norepinephrine should be administered.

7. Extravasation - Dopamine should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the actecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

8. Occlusive vascular disease - Patients with a history of occlusive vascular disease (for example, atheroscierosis, arterial embolism, and Raynaud's disease, cold injury, diabetic endarteritis, and Buergers disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued DOPAMINE infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT - Antidote for Peripheral Ischemia - To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 mL of saline solution containing from 5 to 10 mg of phentolamine mesylate, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

9. Weaning - When discontinuing the infusion, it may be necessary to gradually decrease the dose of dopamine HCl while expanding blood volume with IV fluids, since sudden cessation may result in marked hypotension.

4.5 Interaction with other FPP's and other forms of Interaction

1. Because dopamine is metabolized by monoamine oxidase (MAO), inhibition of this enzyme prolongs and potentiates the effect of dopamine. Patients who have been treated with MAO inhibitors within two to three weeks prior to the administration of dopamine should receive initial doses of dopamine HCl not greater than one-tenth (1/10) of the usual dose.
2. Concurrent administration of low-dose dopamine HCl and diuretic agents may produce an additive or potentiating effect on urine flow.
3. Tricyclic antidepressants may potentiate the cardiovascular effects of adrenergic agents.
4. Cardiac effects of dopamine are antagonized by beta-adrenergic blocking agents, such as propranolol and metroprolol. The peripheral vasoconstriction caused by high doses of dopamine HCl is antagonized by alpha-adrenergic blocking agents. Dopamine-induced renal and mesenteric vasodilation is not antagonized by either alpha- or beta-adrenergic blocking agents.
5. Haloperidol appears to have strong central antidopaminargic properties. Haloperidol and Haloperidol like drugs suppress the dopaminargic renal and masentaric vasodilation induced at low rates of dopamine infusion.
6.Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and may sensitize the myocardium to the action of certain intravenously administered catecholamines, such as dopamine. The interaction appears to be related both to pressor activity and to the beta adrenergic stimulating properties of these catecholamines, and may produce ventricular arrhythmias. Therefore, EXTREME CAUTION should be exercised when administering dopamine HCl to patients receiving cyclopropane or halogenated hydrocarbon anesthetics. Results of studies in animals indicate that dopamine induced ventricular arrhythmias during anesthesia can be reversed by propranolol.
7. The concomitant use of vasopressors, vasoconstricting agents (such as ergonovine) and some oxytocic drugs may result in severe hypertension.
8. Administration of phenytoin to patients receiving dopamine HCl has been reported to lead to hypotension and bradycardia. It is suggested that in patients receiving dopamine HCl, alternatives to phenytoin should be considered if anticonvulsant therapy is needed.

4.6 Pregnancy

Teratogenic Effects: Pregnancy Category C

Animal studies have revealed no evidence of teratogenic effects due to dopamine. However, in one study, administration of dopamine HCl to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. There are no adequate and well-controlled studies in pregnant women and it is not known if dopamine crosses the placental barrier. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if, in the judgment of the physician, the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

In obstetrics, if vasopressor drugs are used to correct hypotension or are added to a local anesthetic solution, some oxytocic drugs may cause severe persistent hypertension and may even cause rupture of a cerebral blood vessel to occur during the postpartum period.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dopamine HCl is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established. Dopamine HCl has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

Cardiovascular System:

- ventricular arrhythmia,
- atrial fibrillation
- ectopic beats,
- tachycardia,
- anginal pain,
- palpitation,
- cardiac conduction abnormalities,

- widened QRS complex,
- bradycardia,
- hypotension,
- hypertension,
- vasoconstriction

Respiratory System:

- Dyspnea

Gastrointestinal System:

- nausea,
- vomiting

Metabolic/Nutritional System:

- Azotemia

Central Nervous System:

- headache,
- anxiety

Dermatological System:

- Piloerection

Other: Gangrene of the extremities has occurred when high doses were administered for prolonged periods or in patients with occlusive vascular disease receiving low doses of dopamine HCl.

4.9 Overdose

In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue dopamine Injection until patient's condition stabilizes. Since the duration of action of dopamine injection is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dopamine is a natural catecholamine formed by the decarboxylation of 3,4-dihydroxyphenylalanine (DOPA). It is a precursor to norepinephrine in noradrenergic nerves and is also a neurotransmitter in certain areas of the central nervous system, especially in the nigrostriatal tract, and in a few peripheral sympathetic nerves.

Dopamine produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adrenoceptors and indirectly by causing release of norepinephrine from storage sites in sympathetic nerve endings.

Dopamine's onset of action occurs within five minutes of intravenous administration, and with dopamine's plasma half-life of about two minutes, the duration of action is less than ten minutes. If monoamine oxidase (MAO) inhibitors are present, however, the duration may increase to one hour. The drug is widely distributed in the body but does not cross the blood-brain barrier to a significant extent. Dopamine is metabolized in the liver, kidney, and plasma by MAO and catechol-O-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid. About 25% of the dose is taken up into specialized neurosecretory vesicles (the adrenergic nerve terminals), where it is hydroxylated to form norepinephrine. It has been reported that about 80% of the drug is excreted in the urine within 24 hours, primarily as HVA and its sulfate and glucuronide conjugates and as 3,4-dihydroxyphenylacetic acid. A very small portion is excreted unchanged.

The predominant effects of dopamine are dose-related, although actual response of an individual patient will largely depend on the clinical status of the patient at the time the drug is administered. At low rates of infusion (0.5-2 mcg/kg/min) dopamine causes vasodilation that is presumed to be due to a specific agonist action on dopamine receptors (distinct from alpha and beta adrenoceptors) in the renal, mesenteric, coronary, and intracerebral vascular beds. At these dopamine receptors, haloperidol is an antagonist. The vasodilation in these vascular beds is accompanied by increased glomerular filtration rate, renal blood flow, sodium excretion, and urine flow. Hypotension sometimes occurs. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolarity of the urine.

At intermediate rates of infusion (2-10 mcg/kg/min) dopamine acts to stimulate the beta1-adrenoceptors, resulting in improved myocardial contractility, increased SA rate and enhanced impulse conduction in the heart. There is little, if any, stimulation of the beta2-adrenoceptors (peripheral vasodilation). Dopamine causes less increase in myocardial oxygen consumption than isoproterenol, and its use is not usually associated with a tachyarrhythmia. Clinical studies indicate that it usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Blood flow to the peripheral vascular beds may decrease while mesenteric flow increases due to increased cardiac output. At low and intermediate doses, total peripheral resistance (which would be raised by alpha activity) is usually unchanged.

At higher rates of infusion (10-20 mcg/kg/min) there is some effect on alpha-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses they are also evident in the renal

and mesenteric vessels. At very high rates of infusion (above 20 mcg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs and override the dopaminergic effects of dopamine, reversing renal dilation and natriuresis.

5.2 Pharmacokinetic properties

Absorption:

Orally administered dopamine is rapidly metabolised in the G.I. tract. Following IV administration, the onset of action of dopamine occurs within 5 minutes, and the drug has duration of action of less than 10 minutes.

Distribution:

The drug is widely distributed in the body but does not cross the blood-brain barrier to a substantial extent. It is not known if dopamine crosses the placenta.

Elimination:

Dopamine has a plasma half-life of about 2 minutes. Dopamine is metabolised in the liver, kidneys, and plasma by monoamine oxidase (MAO) and catechol-0-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3, 4-dihydroxyphenylacetic acid. In patients receiving MAO inhibitors, the duration of action of dopamine may be as long as 1 hour. About 25% of a dose of dopamine is metabolised to norepinephrine within the adrenergic nerve terminals.

Dopamine is excreted in urine principally as HVA and its sulfate and glucuronide conjugates and as 3, 4-dihydroxyphenylacetic acid. A very small fraction of a dose is excreted unchanged. Following administration of radio labelled dopamine, approximately 80% of the radioactivity reportedly is excreted in urine within 24 hours.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber

6 PHARMACEUTICAL PARTICULARS

6.3 List of excipients

Sodium Metabisulfite

Hydrochloric acid

Water for Injection

6.2 Incompatibilities

Dopamine Injection should not be added to any alkaline intravenous solutions, i.e. sodium bicarbonate. Any solution which exhibits physical or chemical incompatibility through a colour change or precipitate should not be administered.

It is suggested that admixtures containing gentamicin sulfate, cephalothin sodium, cephalothin sodium neutral or oxacillin sodium should be avoided unless all other viable alternatives have been exhausted.

Admixtures of ampicillin and dopamine in 5% glucose solution are alkaline and incompatible and result in decomposition of both drugs. They should not be admixed.

Admixtures of dopamine, amphotericin B in 5% glucose solution are incompatible as a precipitate forms immediately on mixing.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

5 ml amber glass ampoule with yellow band snap off.

Blister of 5 Ampoules are placed in amonocarton along with pack insert.

6.6 Special precautions for disposal and other handling

For single use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Do not use if the solution is discoloured.

Preparation of Infusion Solutions

Dilution:

Aseptically transfer Dopamine Sterile Concentrate into the IV solution as shown in the following table:

Strength of Concentrate	Volume of concentrate ml	IV Solution Volume ml	Final Concentration microgram/ml
200 mg/5 ml	5	500	400
200 mg/5 ml	5	250	800

200 mg/5 ml	10	250	1600
200 mg/5 ml	20	500	1600
800 mg/5 ml	5	500	1600
800 mg/5 ml	5	250	3200

Dopamine hydrochloride can be diluted with: -

Sodium chloride (0.9%) intravenous infusion

Dextrose (5%), sodium chloride (0.45%) solution

Sodium lactate intravenous infusion, compound (Hartmann's Solution for Injection)

7. MARKETING AUTHORIZATION HOLDER
M/S VHB MEDI SCIENCES LTD.

50 AB, Govt industrial Estate,

Charkop, Kandivali (W)

Mumbai-400067, INDIA

Manufacturing site:

VHB MEDI SCIENCES LTD.

Plot No.20-22 & 49-51, IIE, Sector-5,

SIDCUL, Pantnagar, Udham Singh Nagar,

Uttarakhand, INDIA.

Tel. No.: +912241639000

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