Dopamine Hydrochloride Injection USP 400mg/10ml, 200mg/5ml.

1. Name of the medicinal product

Dopamine Hydrochloride injection USP 400mg/10ml Taj pharma.

Dopamine Hydrochloride injection USP 200mg/5ml Taj pharma.

2. Qualitative and quantitative composition

a)Dopamine Hydrochloride injection USP 400mg/10ml.
Each ml contains:
Dopamine Hydrochloride 40mg (equivalent to 32.3mg Dopamine Base),

Sodium metabisulfite	9mg
Citric acid	10mg
Sodium Citrate	5mg
Water for Injection	q.s

b)Dopamine Hydrochloride injection USP 200mg/5ml.
Each ml contains:
Dopamine Hydrochloride 40mg (equivalent to 32.3mg Dopamine Base),

Sodium metabisulfite	**9mg**
Citric acid	**10mg**
Sodium Citrate	**5mg**
Water for Injection	**q.s**

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate for solution for infusion

Clear, colourless or pale yellow solution

4. Clinical particulars

4.1 Therapeutic indications
For the correction of haemodynamic imbalances in low-perfusion circulatory insufficiency associated with myocardial infarction, trauma, septicaemia, cardiac failure and open heart surgery.

4.2 Posology and method of administration
Posology

Adults: Use as large a vein as possible for infusion. The initial rate of infusion is 2 to 5 micrograms per kilogram bodyweight per minute and this may be increased gradually by increments of 5 to 10 micrograms/kg/minute until the optimum dose for the individual is achieved. Up to 50 micrograms/kg/minute may be required, and even higher doses have been used.

Paediatric population

The safety and efficacy of dopamine hydrochloride therapy in children have not been established.

Method of administration:

For intravenous use

The solution must be diluted before administration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

A suitable metering device is required in the infusion system to control the rate of flow, and this should be adjusted to the optimum patient response and monitored constantly in the light of the individual patient's response.

4.3 Contraindications
Dopamine should not be used in patients with –

• Hypersensitivity to dopamine or any of the excipients listed in section 6.1.

• Phaeochromocytoma or hyperthyroidism

Dopamine should not be used in the presence of uncorrected atrial or ventricular tachyarrhythmias or ventricular fibrillation.

Cyclopropane and halogenated hydrocarbon anaesthetics should be avoided.

4.4 Special warnings and precautions for use
Warnings:

Patients who have been treated with MAO inhibitors prior to dopamine should be given

reduced doses; the starting dose should be one tenth (1/10th) of the usual dose.

Excess administration of potassium-free solutions may result in significant hypokalaemia.

The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary oedema.

Precautions:

Hypovolaemia should be corrected where necessary prior to dopamine infusion. Low doses should be used in shock due to acute myocardial infarction.

If a disproportionate rise in diastolic pressure (i.e. a marked decrease in pulse pressure) is observed, the infusion rate should be decreased and the patients observed carefully for further evidence of predominant vasoconstriction activity, unless such an effect is desired.

Patients with a history of peripheral vascular disease should be closely monitored for any changes in colour or temperature of the skin of the extremities. If change of skin colour 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. These changes may be reversed by decreasing the rate or discontinuing the infusion. IV administration of phentolamine mesylate 5-10 mg may reverse the ischaemia.

Dopamine hydrochloride in 5% Glucose injection should be infused into a large vein whenever possible to prevent the possibility of infiltration of perivascular tissue adjacent to the infusion site. Extravasation of dopamine hydrochloride during infusion may cause ischaemic necrosis and sloughing of surrounding tissue. Ischaemia can be reversed by infiltration of the affected area with 10-15 ml of saline containing 5 to 10 mg phentolamine mesylate. A syringe with a fine hypodermic needle should be used to liberally infiltrate the ischaemic area as soon as extravasation is noted.

Administration of dopamine hydrochloride should always be under the direct supervision of a physician to whom facilities are available for monitoring cardiovascular and renal indices, including blood volume, cardiac output, blood pressure, electrocardiography and urine flow.

Glucose solutions should be used with caution in patients with known subclinical or overt diabetes mellitus.

When dopamine is used in patients with a history of occlusive vascular disease, particular attention should be paid to the status of blood circulation in the extremities.

The occurrence of undesirable increases in blood pressure or vasoconstriction or decrease in urinary output requires a reduction in dosage of dopamine hydrochloride.

The routine use of low-dose dopamine hydrochloride in critically ill patients to prevent or treat acute renal failure is not recommended because this may cause adverse effects which could further compromise such patients.

As the effect of dopamine on impaired renal and hepatic function is not known, close monitoring is advised.

Dopamine infusion should be withdrawn gradually, to avoid unnecessary hypotension.

Dopamine Hydrochloride 40mg/ml Concentrate for Solution for Infusion contains an antioxidant, sodium metabisulfite, a sulphite that may cause allergic-type reactions including bronchospasm, anaphylaxis and life- threatening episodes in certain susceptible individuals. The prevalence of sulphite-sensitivity in the general population is unknown and is probably low.

Sulphite-sensitivity is seen more frequently in persons with a history of asthma or atopic allergy.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
i) Anaesthetics:

The myocardium is sensitised by the effect of dopamine, cyclopropane or halogenated hydrocarbon anaesthetics, and these should be avoided. This interaction applies both to pressor activity and cardiac beta adrenergic stimulation.

ii) Alpha and Beta Blockers:

The cardiac effects of dopamine are antagonised by β -adrenergic blocking agents such as propanolol and metoprolol, and the peripheral vasoconstriction caused by high doses of dopamine is antagonised by α adrenergic blocking agents. Dopamine induced renal and mesenteric vasodilation is not antagonised by either α or β- adrenergic blocking agents, but, in animals, is antagonised by haloperidol or other butrophenones, phenothiazines and opiates.

iii) Monoamine Oxidase (MAO) Inhibitors:

MAO inhibitors potentiate the effect of dopamine and its duration of action. Patients who have been treated with MAO inhibitors prior to administration of dopamine will therefore require a substantially reduced dosage. (The starting dose should be reduced to at least 1/10th of the usual dose).

iv) Phenytoin:

Administration of IV phenytoin to patients receiving dopamine has resulted in hypotension and bradycardia; some clinicians recommend that phenytoin be used with extreme caution, if at all, in patients receiving dopamine.

Dopamine may increase the effect of diuretic agents.

The ergot alkaloids should be avoided because of the possibility of excessive vasoconstriction. Tricyclic antidepressants and guanethidine may potentiate the pressor response to dopamine.

4.6 Fertility, pregnancy and lactation
Pregnancy

Animal studies have shown no evidence of teratogenic effects with dopamine.

However, the effect of dopamine on the human foetus is unknown. Therefore the drug should be used in pregnant women only when the expected benefits outweigh the potential risk to the foetus.

Lactation

It is not known if dopamine is excreted in breast milk, nor is the effect on the infant known.

Fertility

No data available.

4.7 Effects on ability to drive and use machines
Not applicable in view of the indications for use and the short half-life of the drug.

4.8 Undesirable effects
Adverse reactions to dopamine are related to its pharmacological action.

The following adverse reactions are classified by system organ class and ranked under heading of frequency: Common (>1/100 to <1/10; Uncommon (≥1/1,000 to <1/100).

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Common	Headache
	Uncommon	Piloerection
Eye disorders	Uncommon	Mydriasis
Cardiac disorders	Common	Ectopic heart beats, tachycardia, anginal pain, palpitation, hypotension, vasoconstriction.
	Uncommon	Aberrant conduction, bradycardia, widened QRS complex, hypertension, gangrene, fatal ventricular arrhythmias have been reported on rare occasions.

Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Nausea, vomiting
Renal and urinary disorders	Uncommon	Azotaemia

Serious or Life-threatening Reactions:

Gangrene of the feet has occurred following doses of 10-14 microgram/kg/min and higher in a few patients with pre-existing vascular disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose
Excessive elevation of blood pressure and vasoconstriction can occur due to the alpha adrenergic actions of dopamine, especially in patients with a history of occlusive vascular disease. If desired, this condition can be rapidly reversed by dose reduction or discontinuing the infusion, since dopamine has a half-life of less than 2 minutes in the body.

Should these measures fail, an infusion of an alpha adrenergic blocking agent, e.g., phentolamine mesylate, should be considered.

Dopamine at the infusion site can cause local vasoconstriction hence the desirability of infusing into a large vein. The resulting ischaemia can be reversed by infiltration of the affected area with 10-15 ml of saline containing 5 mg to 10 mg phentolamine mesylate. A syringe with a fine hypodermic needle should be used to liberally infiltrate the ischaemic area as soon as extravasation is noted.

Accidental Overdosage:

Accidental overdosage as evidenced by excessive blood pressure elevation can be controlled by dose reduction or discontinuing the dopamine infusion for a short period, since the duration of action of dopamine is short.

Should these measures fail, an infusion of phentolamine mesylate should be considered.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: adrenergic and dopaminergic agents

Dopamine (3,4-dihydroxyphenylethylamine) is the third naturally occurring catecholamine and is a metabolic precursor of noradrenaline and adrenaline. Dopamine is used therapeutically as the hydrochloride and its main effects are seen in the cardiovascular system and the kidneys.

Mechanism of action

Heart

Dopamine exerts positive inotropic and chronotropic effects on the myocardium, acting as an agonist at beta-adrenergic receptors. In addition to its direct action on beta-adrenergic receptors, dopamine acts indirectly by releasing noradrenaline from sympathetic storage sites.

Blood Vessels

Depending on the vascular bed being studied and the dose administered, Dopamine can cause relaxation or contraction of vascular smooth muscle.

Pharmacodynamic effects

Dopamine Receptors

Unlike other endogenous catecholamines or sympathomimetic amines, Dopamine caused vasodilation in renal, coronary, mesenteric and intracerebral arterial vascular beds in anaesthetised dogs. This vasodilator effect is not antagonised by beta-adrenergic blockers, atropine or antihistamines. However, butyrophenones, phenothiazines, apomorphine and bulbocapnine selectively attenuate dopamine-induced vasodilatation, thus suggesting the existence of specific dopamine vascular receptors similar to those in the basal

ganglia and other areas in the central nervous system.

Alpha-adrenergic Receptors

Dose response studies indicate that with a sufficiently large dose, the vasoconstrictor effect of dopamine predominates over its vasodilator effect. This dopamine-induced vasoconstrictor effect is antagonised by alpha-adrenoreceptor blocking agents such as phentolamine and phenoxybenzamine, indicating that vasoconstriction results from the action of dopamine on alpha-adrenergic receptors.

Kidney

Intravenous infusions of dopamine (2.6 to 7.1µg/kg/min) to seven normal subjects increased estimated average renal plasma flow from 507 to 798ml/min, inulin clearance from 109 to 136ml/min and average sodium excretion from 171 to 571µEq./min. Although the diuretic and natriuretic effects of dopamine may result from vasodilatation in renal vascular bed (vide supra), disassociation between natriuresis and increments in renal blood flow has been observed, suggesting that other mechanisms such as redistribution of intrarenal blood flow may be involved.

5.2 Pharmacokinetic properties
Dopamine is inactive when taken orally and its vasoconstrictor properties preclude its administration by subcutaneous or intramuscular injection. Dopamine hydrochloride is administered by intravenous infusion

Biotransformation and Elimination

Dopamine is a metabolic precursor of noradrenaline and, whereas a proportion is excreted as the metabolic products of noradrenaline.

The plasma half-life of dopamine is approximately two 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 which are rapidly excreted in the urine. 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
No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium Metabisulfite

Water for Injections

6.2 Incompatibilities
Iron salts, alkalis or oxidising agents.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'

6.3 Shelf life
36 months

For single use only If only part of an ampoule is used, discard the remaining solution.

Diluted solutions should be used immediately. Discard any remaining solution

6.4 Special precautions for storage
Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container
5 ml clear glass one point-cut (OPC) ampoules, glass Type I Ph Eur. borosilicate glass ampoules packed in cardboard cartons to contain 10 x 5ml ampoules.

6.6 Special precautions for disposal and other handling

This solution must be diluted before use.

Do not dilute with alkaline solution.

Inspect the solution before use. Do not use the injection if it is darker than slightly yellow or discoloured in any other way or if it contains particulate matter.

Alkaline solutions such as 5% sodium bicarbonate should NOT be added to dopamine hydrochloride because the drug will be inactivated. The usual dilution is 1,600 micrograms per ml and this may be achieved by transfer, aseptically of 800mg of dopamine hydrochloride (20 ml of the Dopamine Hydrochloride 40mg/ml Concentrate for Solution for Infusion) to 480 ml one of the following sterile I.V. solutions to achieve 1,600 microgram per ml concentration:

Sodium Chloride Injection

5% Glucose Injection

5% Glucose and 0.9% Sodium Chloride Injection

5% Glucose and 0.45% Sodium Chloride Solution

5% Glucose in Ringer Lactate Solution

Sodium Lactate 1/6 Molar Injection

Lactated Ringer's Injection

7.Manufactured in India by:
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Maharashtra chambers of Commerce Lane,
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