SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dopamine 40 mg/ml, Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 40 mg dopamine hydrochloride.

Each 5 ml ampoule of concentrate contains 200 mg dopamine hydrochloride.

The solution has pH between 2.5 – 5.0 and osmolality is around 560 mOsm/kg.

Excipient(s) with known effect: sodium metabisulphite (E223). This excipient may rarely cause severe hypersensitivity reactions and bronchospasm.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Ampoules containing a clear colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dopamine is indicated in adults for the correction of haemodynamic imbalance present in:

- Acute hypotension or shock associated with myocardial infarction, endotoxic septicaemia and trauma.
- As an adjunct after open heart surgery where there is persistent hypotension after correction of hypovolaemia.
- Acute exacerbations of chronic heart failure where is low cardiac output.

4.2 Posology and method of administration

Posology

Adults

Where appropriate, the circulating blood volume must be restored with a suitable plasma expander or whole blood, prior to administration of dopamine hydrochloride.

Begin infusion of dopamine hydrochloride solution at doses of 2.5 microgram/kg/min in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more severe cases, administration may be initiated at a rate of 5 microgram/kg/min and increased gradually in 5 to 10 microgram/kg/min increments up to 20 to 50 microgram/kg/min as needed. If doses in excess of 50 microgram/kg/min are required, it is advisable to check urine output frequently.

Should urinary flow begin to decrease in the absence of hypotension, reduction of dopamine dosage should be considered. It has been found that more than 50% of patients have been satisfactorily maintained on doses less than 20 microgram/kg/min.

In patients who do not respond to these doses, additional increments of dopamine may be given in an effort to achieve adequate blood pressure, urine flow and perfusion generally.

Treatment of all patients requires constant evaluation of therapy in terms of blood volume, augmentation of cardiac contractility, and distribution of peripheral perfusion and urinary output.

Dosage of dopamine should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indications for decreasing or temporarily suspending the dosage.

Patients who have been treated with MAO inhibitors 2-3 weeks prior to administration of dopamine require a substantially reduced dosage. (The starting dose should be reduced to at least $^{1}/_{10}$ of the usual dose.

Paediatric population

The safety and efficacy of dopamine in paediatric patients has not been established.

Elderly

In clinical trials with parenteral Dopamine, the number of patients aged 65 years or older included was not sufficient to determine if they behave differently from younger patients. Generally, dose selection in elderly patients should be cautious and an initial lower dose is regularly used.

Close monitoring is suggested for blood pressure, urine flow and peripheral tissue perfusion.

Method of administration:

To be administered by intravenous infusion only after dilution with the appropriate diluents.

Dopamine hydrochloride should be infused into a large vein whenever possible, preferably with an infusion syringe pump system. Special care should be given to the perfusion rate in order to avoid inadvertent boluses.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Dopamine should not be used in patients with phaeochromocytoma.

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

4.4 Special warnings and precautions for use

Dopamine should not be used in patients with hyperthroidism.

Cyclopropane and halogenated hydrocarbon anaesthetics should be avoided.

Dopamine should be used with caution in patients with narrow angle glaucoma.

Dopamine should be used with caution in patients with benign prostatic hyperplasia with urinary retention.

Patients who have been treated with MAO inhibitors prior to dopamine should be given reduced doses; the starting dose should be one tenth ($^{1}/_{10}$) 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.

Dopamine hydrochloride should not be added to sodium bicarbonate or other alkaline solution as drug inactivation will occur.

Conditions like hypoxia, hypercapnia and acidosis can reduce dopamine efficacy and/or increase the incidence of adverse events and should therefore identified and corrected before or during administration of Dopamine hydrochloride.

Regular clinical and biochemical assessment is necessary to monitor changes in fluid, electrolyte or acid-base status during prolonged treatment and whenever the patient

condition demands it. During treatment with Dopamine hydrochloride, blood pressure, heart rate, urine output, EKG and cardiac output should be monitored.

If tachyarrhythmias or increase in ectopic beats are observed, Dopamine hydrochloride should be reduced, if possible.

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.

Dopamine hydrochloride should be infused into a large vein whenever possible to prevent the possibility of infiltration of perivascular tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of the 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.

Dopamine should be used with extreme caution in patients inhaling cyclopropane or halogenated hydrocarbon anaesthetics due to the arrhythmogenic potential.

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

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, concentrate for solution for infusion, contains sodium metabisulfite, excipient that can cause allergic reactions including anaphylactic symptoms and life-threatening, or episodes of less severe asthma, in susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. This sensitivity is seen more frequently in asthmatic population than in non-asthmatic.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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.

The cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines, like dopamine. This interaction seems to be related to both pressor activity as with beta-adrenergic stimulating properties of these catecholamines, may cause ventricular arrhythmias and hypertension. Therefore, as with other catecholamines, and due to its theoretical arrhythmogenic potential, dopamine must be administered with extreme caution in patients receiving inhalation anesthetics cyclopropane or halogenated hydrocarbon. The results of animal studies indicate that ventricular arrhythmias induced by the Dopamine during anesthesia can be reversed by propranolol.

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.

Monoamine Oxidase (MAO) Inhibitors:

MAO inhibitors potentiate the effect of dopamine and its duration of action. In patients receiving MAO inhibitors, the duration of action of dopamine may be as long as 1 hour. 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 $^{1}/_{10}$th of the usual dose.

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.

Reserpin, cardiac glucosides, metoclopramide.

The risk of arrhythmias is greater in patients taking drugs that impact to the conduction in the heart, thyroid hormones, cardiac glycosides and antiarrhythmics.

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. Because many drugs are excreted in human milk, caution should be exercised when dopamine HCl is administered to a nursing woman.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not applicable, as the drug product is to be administered at the hospital.

4.8 Undesirable effects

Adverse reactions to dopamine are related to its pharmacological action. The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

More common reactions include

Cardiovascular:	Ectopic heart beats, tachycardia, anginal pain, palpitation, hypotension and vasoconstriction.
Gastrointestinal:	Nausea and vomiting.
Nervous System:	Headache, anxiety, tremor.
Respiratory:	Dyspnea.
Renal and urinary disorders:	Polyuria.
Investigations:	Serum glucose level increased, BUN level increased.

Less common reactions include

Biochemical Abnormalities:	Azotemia.
Cardiovascular:	Aberrant conduction, bradycardia, widened QRS complex, hypertension, gangrene, fatal ventricular

	arrhythmias have been reported on rare occasions.
Eye Disorders:	Mydriasis.
Nervous System:	Piloerection.

Serious or Life-threatening Reactions:

Gangrene of the extremities has occurred following higher doses and in lower doses patients with pre-existing vascular disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.3 Sympathomimetic, ATC code: C01CA04 dopamine

Dopamine stimulates adrenergic receptors of the sympathetic nervous system. The drug has principally a direct stimulatory effect on β_1-adrenergic receptors, but also appears to have an indirect effect by releasing norepinephrine from its storage sites. Dopamine also appears to act on specific dopaminergic receptors in the renal, mesenteric, coronary, and intracerebral vascular beds to cause vasodilation. The drug has little or no effect on β_2-adrenergic receptors.

In IV doses of 0.5-2 microgram/kg per minute, the drug acts predominantly on dopaminergic receptors; in IV doses of 2-10 microgram/kg per minute, the drug also stimulates β_1-adrenergic receptors. In higher therapeutic doses, α-adrenergic receptors are stimulated and the net effect of the drug is the result of α-adrenergic, β_1-adrenergic, and dopaminergic stimulation. The main effects of dopamine depend on the dose administered. In low doses, cardiac stimulation and renal vascular dilation occur and in larger doses vasoconstriction occurs. It is believed that α-adrenergic

effects result from inhibition of the production of cyclic adenosine -31, 51-monophosphate (cAMP) by inhibition of the enzyme adenyl-cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity.

Clinical studies showed that the product generally increases systolic and pulse, with no effect or only a slight increase of diastolic pressure. Total peripheral resistance does not usually undergo changes with the administration of low doses of dopamine or medium. The blood flow in the peripheral vasculature may decrease, whereas the mesenteric blood flow increases. It has also been noted that the product causes dilatation of renal vasculature, which is accompanied by an increase in glomerular filtration rate, renal blood flow and sodium excretion.

Following IV administration, the onset of action of dopamine occurs within 5 minutes, and the drug has a duration of action of less than 10 minutes.

5.2 Pharmacokinetic properties

Absorption

Following IV administration the maximum plasma concentration is reached within a few 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.

Biotransformation

Dopamine is metabolised in the liver, kidneys, and plasma by monoamine oxidase (MAO) and catechol-0-methyltransferase (COMT) 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.

Elimination

Dopamine has a plasma half-life of about 2 minutes. Dopamine is excreted in urine principally as HVA and its sulphate and glucuroide 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

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. Besides this study, there are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections

6.2 Incompatibilities

Dopamine concentrate for solution for infusion, 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 sulphate, 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

3 years

In-use stability:

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (< 25ºC).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2º to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml clear, type I glass one point-cut (OPC) ampoules, packed in cardboard cartons.

Pack size: 10 ampoules

6.6 Special precautions for disposal

For single use.

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

Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration. Do not use if the injection is darker than slightly yellow or discoloured in any other way.

Preparation of Infusion Solutions

Suggested Dilution

Aseptically transfer the sterile concentrate for solution for infusion into the IV solution as shown in the following table:

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

Dopamine hydrochloride can be diluted with:

- 0.9% Sodium Chloride Injection
- 5% Glucose Injection
- 5% Glucose and 0.9% Sodium Chloride Injection
- 0.45% Sodium Chloride Solution
- 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 MARKETING AUTHORISATION HOLDER

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