Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dopamine 160 mg/ml Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 160mg dopamine hydrochloride.

Each 5 ml of concentrate contains 800mg of dopamine hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Ampoules containing a clear colourless or pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

a) Acute hypotension or shock associated with myocardial infarction, endotoxic septicaemia, trauma and renal failure.

b) As an adjunct after open heart surgery, where there is persistent hypotension after correction of hypovolaemia.

c) In chronic cardiac decompensation as in congestive failure.

4.2 Posology and method of adminstration

Dopamine is a potent drug; it must be diluted before administration.

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 mcg/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 5mcg/kg/min and increased gradually in 5 to 10mcg/kg/min increments up to 20 to 50mcg/kg/min as needed. If doses in excess of 50mcg/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 20mcg/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.

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

GERIATRIC
No variation in dosage is suggested for geriatric patients. However, close monitoring is suggested for blood pressure, urine flow and peripheral tissue perfusion.

4.3 Contraindications

Dopamine should not be used in patients with phaeochromocytoma or hyperthyroidism.

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

Cyclopropane and halogenated hydrocarbon anaesthetics should be avoided.

4.4 Special warnings and precautions for use

Warnings:
Dopamine should not be used in the presence of uncorrected tachyarrhythmias or ventricular fibrillation. Nor should it be used in patients with phaeochromocytoma or hyperthyroidism. Cyclopropane and halogenated hydrocarbon anaesthetics should be avoided.

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 a 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% dextrose 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 may cause necrosis and sloughing of the surrounding tissue. Ischaemia can be reversed by infiltration of the affected area with 10-15ml of saline containing 5 to 10mg 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 arterial 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.

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 ß-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 ß-adrenergic blocking agents, but, in animals, is antagonised by haloperidol or other butyrophenones, 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 monoamine oxidase (MAO) inhibitors prior to dopamine should be given reduced doses; the starting dose should be one tenth ($1/10^{th}$) of the usual dose.

iv) *Phenytoin*
Administration of I.V. 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.

4.6 Pregnancy and lactation

Use in 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.

Use in Lactation:
It is not known if dopamine is excreted in breast milk, nor if there is any effect on the infant.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse reactions to dopamine are related to its pharmacological action.

More Common Reactions Include:

Cardiovascular: Ectopic beats, tachycardia, anginal pain, palpitation, hypotension, vasoconstriction.

Gastrointestinal: Nausea, vomiting.

Nervous System: Headache.

Respiratory: Dyspnoea.

Less Common Reactions include:

Biochemical Abnormalities: Azotaemia.

Cardiovascular: Aberrant conduction, bradycardia, widened QRS complex, hypertension, gangrene, cardiac arrhythmias have been reported on rare occasions.

Eye disorders: Mydriasis.

Nervous system: Piloerection.

Serious or Life-threatening Reactions:

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

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 10-15ml of saline containing 5mg to 10mg 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

Dopamine stimulates adrenergic receptors of the sympathetic nervous system. The drug has principally a direct stimulatory effect on $ß_1$-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 $ß_2$-adrenergic receptors.

In I.V. doses of 0.5-2µg/kg per minute, the drug acts predominantly on dopaminergic receptors; in I.V. doses of 2-10µg/kg per minute, the drug also stimulates $ß_1$-adrenergic receptors. In higher therapeutic doses, α-adrenergic receptors are stimulated and the net effect of the drug is the result of α-adrenergic, $ß_1$-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-3'5'-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas ß-adrenergic effects result from stimulation of adenyl cyclase activity.

5.2 Pharmacokinetic properties

Absorption:
Orally administered dopamine is rapidly metabolised in the G.I. tract. Following I.V. administration, the onset of action of dopamine occurs within 5 minutes, and the drug has a 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 sulphate 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 which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite
Water for Injections

6.2 Incompatibilities

Sterile Dopamine Concentrate 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

As packaged for sale: 3 years.

In-use: Following dilution in the recommended diluents (see Section 6.6), chemical and physical in-use stability has been demonstrated for 48 hours at a temperature not above 25°C.

However, 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 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale: Do not store above 30°C. Keep container in the outer carton.

In use: See 6.3.

6.5 Nature and contents of container

Clear, type I, glass ampoules. Pack Size: 5's.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use. Discard any unused contents.
Do not use if the solution is discoloured.

Preparation of Infusion Solutions

Suggested 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 AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 437/3/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 May 1986
Date of last renewal: 21 May 2001

10 DATE OF REVISION OF THE TEXT

October 2003