Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 12.5 mg of dobutamine (as dobutamine hydrochloride).

Each 20 ml presentation contains 250 mg of dobutamine (as dobutamine hydrochloride).

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
Clear, colourless or slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dobutamine hydrochloride is a sympathomimetic agent, which acts by stimulating the beta-1 adrenergic receptors of the heart promoting a prominent inotropic action on the heart, increasing cardiac contractility and stroke volume. It is a direct acting agent.

Dobutamine is indicated for adults who require inotropic support in the treatment of low output cardiac failure associated with organic heart disease, myocardial infarction, open heart surgery, cardiomyopathies, septic shock and cardiogenic shock. Dobutamine can increase or maintain cardiac output during positive end expiratory pressure (PEEP) ventilation.

Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.

4.2 Posology and method of administration

Dobutamine should be diluted before use and administered by IV infusion only.

Administration

The concentration of dobutamine administered depends upon the dosage and fluid requirements of the individual patient. Concentrations of 5000 micrograms/ml have been used in fluid restricted patients but this concentration should not be exceeded. High concentrations of dobutamine should only be given with an infusion pump to ensure accurate dosage. Due to its short half-life dobutamine should be administered as a continuous intravenous infusion. Dobutamine should be administered intravenously through an intravenous needle or catheter. An intravenous pump or other suitable apparatus should be used to control the flow rate in drops per minute. For information on dilution see **Instructions for Use/Handling**.

Dosage

Adults: **The usual rate is 2.5 to 10 micrograms/kg/min, which should be adjusted according to the patient's heart rate, blood pressure, cardiac output and urine output. Up to 40 micrograms/kg/min may occasionally be**

required, but this is rare. Dobutamine infusions have been given for up to 72 hours without a decrease in effectiveness. It is recommended that treatment with dobutamine should be discontinued gradually.

Side effects which are dose related, are infrequent when dobutamine is administered at rates below 10 micrograms/kg/min. Rates as high as 40 micrograms/kg/min have been used occasionally without significant adverse effects.

Elderly: **No variation in dosage is suggested. Close monitoring is required for blood pressure, urine flow and peripheral tissue perfusion.**

Paediatric population: For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2 – 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute, but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller “therapeutic width” in children.

Method of administration
For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.
Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

4.3 Contraindications

Patients with known or suspected hypersensitivity to dobutamine or sulphites. Patients with marked mechanical obstruction affecting ventricular filling or outflow, or both, such as cardiac tamponade, valvular aortic stenosis or idiopathic hypertrophic subaortic stenosis. Patients with hypovolaemia unless it has been corrected by volume replacement. Patients with chronic heart failure. Decompensation associated with hypertrophic cardiomyopathy.

4.4 Special warnings and precautions for use

If an undue increase in heart rate or systolic blood pressure occurs or if an arrhythmia is precipitated the dose of dobutamine should be reduced or the drug should be discontinued temporarily.

Dobutamine may precipitate or exacerbate ventricular ectopic activity, rarely has it caused ventricular tachycardia or fibrillation. Because dobutamine increases atrioventricular conduction, patients with atrial flutter or fibrillation may develop a rapid ventricular response, and therefore should be digitalised prior to administration of dobutamine.

Experience with the use of dobutamine following acute myocardial infarction is limited. However there is a possibility that dobutamine can cause a significant increase in heart rate or excessive increase in arterial pressure which may intensify or extend myocardial ischaemia, cause anginal pain and ST segment elevation, therefore care should be exercised following myocardial infarction.

Dobutamine will not improve haemodynamics in most patients with mechanical obstruction affecting ventricular filling or outflow, or both.

Inotropic response may be inadequate in patients with markedly reduced ventricular compliance, e.g. with cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis (see **Contraindications**).

Minor vasoconstriction has been observed in patients treated with beta blocking drugs. This may occur due to the inotropic effect of dobutamine which stimulates cardiac beta-1 receptors and which is blocked by beta blockers. Conversely alpha adrenergic blockade may make the beta-1 and beta-2 effects apparent, resulting in tachycardia and vasodilation.

Before administration of dobutamine, hypovolaemia should be corrected with an appropriate plasma volume expander (see **Contraindications**). The ECG, blood pressure and when possible, cardiac output and pulmonary wedge pressure should be monitored.

Like other drugs with beta-2 agonist activity, dobutamine may produce slight reductions in serum potassium concentrations and hypokalaemia may occur occasionally. Consideration should be given to monitoring serum potassium during dobutamine therapy.

During administration of dobutamine heart rate and rhythm, arterial blood pressure, and infusion rate should be monitored closely. When starting therapy, electrocardiographic monitoring is recommended until a stable response is obtained.

Dobutamine should be used with caution in severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70 mm Hg). If the blood pressure drops quickly, decreasing the dose or stopping the infusion typically results in a return to base-line blood pressure values. Occasionally intervention may be required and reversibility may not be immediate.

If arterial blood pressure remains low or decreases progressively during administration of dobutamine despite adequate ventricular filling pressure and cardiac output, consideration may be given to the use of a peripheral vasoconstrictor agent e.g. noradrenaline or dopamine.

Dobutamine Concentrate for Solution for Infusion contains sodium metabisulphite in the formulation. This may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulphite sensitivity in the general population is unknown but is probably low; such sensitivity seems to occur more frequently in asthmatic patients. Patients with bronchial asthma who are hypersensitive to sulfites may develop the following adverse effects: vomiting, diarrhoea, bronchoconstriction, altered states of consciousness and shock.

Dobutamine should only be used under the direct supervision of physicians to whom facilities for regular, intensive monitoring of cardiovascular and renal parameters, in particular, blood volume, myocardial contractility, cardiac output, electrocardiography, urine flow rate, and blood and pulse pressure are available.

Since the effect of dobutamine on impaired renal and hepatic function is not known, close monitoring is advisable.

Intravenous continuous dobutamine is of limited benefit and may in fact be harmful to patients with advanced heart failure, with respect to quality of life and survival rates.

The use of dobutamine as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, bundle branch block or any cardiac condition that could make them unsuitable for exercise stress testing.

Possible complications associated with dobutamine stress echocardiogram include chest pain, severely high blood pressure, arrhythmias and heart attacks (see Section 4.8).

No special measures are required in the event of extravasation, as no vasoconstriction or ischemia has been observed (see section 4.8).

During continuous infusion (48-72 hours), the haemodynamic effect may be reduced, which indicates that higher doses are needed.

It is recommended that precautions be taken in patients with a history of severe ventricular arrhythmia.

Paediatric population

Dobutamine has been administered to children with low-output hypoperfusion states resulting from decompensated heart failure, cardiac surgery, and cardiogenic and septic shock. Some of the haemodynamic effects of dobutamine hydrochloride may be quantitatively or qualitatively different in children as compared to adults. Increments in heart rate and blood pressure appear to be more frequent and intense in children. Pulmonary wedge pressure may not decrease in children, as it does in adults, or it may actually increase, especially in infants less than one year old. The neonate cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect seems to be more often observed in adult patients than in small children.

Accordingly, the use of dobutamine in children should be monitored closely, bearing in mind these pharmacodynamic characteristics.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-Adrenergic blocking agents:
In animals the cardiac effects of dobutamine are antagonised by beta-adrenergic blocking agents such as propranolol and metoprolol, resulting in predominance of alpha-adrenergic blocking agents and increased peripheral resistance.

Conversely, alpha-adrenergic blockade may make the beta 1 and beta 2 effects apparent, resulting in tachycardia and vasodilatation.

The addition of dipyridamole to dobutamine for echocardiography can cause potentially hazardous hypotension. The combination should not be used in patients suspected of coronary heart disease.

General anaesthetics:
Ventricular arrhythmias have been reported in animals receiving usual doses of dobutamine during halothane or cyclopropane anaesthesia; therefore, caution should be exercised when administering dobutamine to patients receiving these anaesthetics.

The concomitant use of dobutamine and sodium nitroprusside or nitroglycerin can cause an increase in cardiac output and a decrease in pulmonary arterial pressure, greater than that produced when each product is administered separately.

Dopamine that contains sodium metabisulfite (an antioxidant) may react with thiamine and cause a reduction in the latter.

4.6 Fertility, pregnancy and lactation

Reproductive studies in rats and rabbits have not revealed any evidence of impaired fertility, evidence of harm to the foetus or teratogenic effects. No data exists that would make it possible to evaluate any harmful effects of dobutamine administration during pregnancy. There have been no studies in humans on use during pregnancy. Dobutamine should not be used in pregnant women unless the possible benefits outweigh the potential risks.

It is not known if dobutamine crosses the placenta or is distributed into milk. Therefore caution should be exercised. If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

4.7 Effects on ability to drive and use machines

There is no data on the influence of this product on the ability to drive or use machines. However, the effect is not predictable.

4.8 Undesirable effects

The adverse reaction listed below is defined using the following MedDRA System Organ Class and frequencies:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare(≥1/10,000 to <1/1,000); Very rare (<1/10,000)

Where no indication of frequency is provided below, this is because the frequency cannot be estimated from the available data.

Cardiac Disorders:
Very common: increased heart rate, palpitation
Uncommon: marked tachycardia together with ventricular ectopic activity, increased ventricular rate (in patients with pre-existing atrial fibrillation), ventricular tachycardia, ventricular fibrillation and arrhythmias

Principal adverse effects are ectopic heart beats, stress cardiomyopathy and angina. All of these cardiovascular effects are usually dose related, and dosage should be reduced or temporarily discontinued if they occur.

In addition to the events described above, patients undergoing dobutamine stress echocardiography may experience severely high blood pressure, dizziness, extreme fatigue, and on occasion, myocardial infarction.

General Disorders and Administration Site Conditions:
Common: non specific chest pain
Rare: phlebitis at the site of the IV infusion has been reported occasionally.

Investigations:
Elevations in systolic pressure, abnormal increase in blood pressure (50mmHg in patients with pre-existing hypertension), as with other catecholamines, decreases in serum potassium concentrations have occurred, rarely to hypokalaemic values.

Blood and Lymphatic System Disorders:
There have been isolated reports of thrombocytopenia.

Gastrointestinal Disorders:
Common: nausea, vomiting

Nervous System Disorders
Common: headache
Tingling sensation, paraesthesia, mild leg cramps.

Immune System Disorders:
Common: hypersensitivity, including rash, fever, eosinophilia and bronchospasm.
Pruritis of the scalp during IV infusion of dobutamine has been reported as with other reactions indicative of hypersensitivity. Hypersensitivity (to sulfites in asthmatic patient may present as bronchospasm and anaphylactic shock).

Respiratory, Thoracic and Mediastinal Disorders:
Common: dyspnoea

Inadvertent subcutaneous infiltration of dobutamine has caused local inflammatory changes and local pain without local ischaemia; dermal necrosis has been reported.

Infusions for up to 72 hours have revealed no adverse effects other than those seen with shorter infusions. There is evidence that partial tolerance develops with continuous infusions of dobutamine for 72 hours or more; therefore higher doses may be required to maintain the same effects.

Paediatric population
The undesirable effects include elevation of systolic blood pressure, systemic hypertension or hypotension, tachycardia, headache, and elevation of pulmonary wedge pressure leading to pulmonary congestion and edema, and symptomatic complaints.

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 national reporting system:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517,
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Overdosage has been reported rarely. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, fatigue and anginal and non-specific chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachyarrhythmias, myocardial ischaemia and ventricular fibrillation. Hypotension may result from vasodilation. The duration of action of dobutamine hydrochloride is generally short (half-life, approximately 2 minutes).

Temporarily discontinue dobutamine until the patient's condition stabilises. The patient should be monitored and any appropriate resuscitative measures started immediately.

Forced diuresis, peritoneal dialysis, haemodialysis or charcoal haemoperfusion have not been established as beneficial.

If the product is ingested, unpredictable absorption may occur from the mouth and gastrointestinal tract.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dobutamine is a selective beta-adrenergic agonist whose mechanism of action is complex.

It is believed that the beta-adrenergic effects result from stimulation of adenyl cyclase activity. In therapeutic doses, dobutamine also has mild beta-2 and alpha-1 adrenergic receptor agonist effects, which are relatively balanced and result in minimal net direct effect on systemic vasculature. Dobutamine does not cause release of endogenous norepinephrine. The main effect of therapeutic doses of dobutamine is cardiac stimulation.

While the positive inotropic effect of the drug on the myocardium appears to be mediated principally via beta-1 adrenergic stimulation, experimental evidence suggests that alpha-1 adrenergic stimulation may also be involved and that the alpha-1 adrenergic activity results mainly from the (-)-stereoisomer of the drug.

The beta-1 adrenergic effects of dobutamine exert a positive inotropic effect on the myocardium and result in an increase in cardiac output due to increased myocardial contractility and stroke volume. Increased left ventricular filling pressure decreases in patients with congestive heart failure. In therapeutic doses, dobutamine causes a decrease in peripheral resistance; however, systolic blood pressure and pulse pressure may remain unchanged or be increased because of augmented cardiac output. With usual doses, heart rate is usually not substantially changed. Coronary blood flow and myocardial oxygen consumption are usually increased because of increased myocardial contractility.

Dobutamine facilitates atrioventricular conduction and shortens or causes no important change in intraventricular conduction. The tendency of dobutamine to induce cardiac arrhythmias may be slightly less than that of dopamine and

is considerably less than that of isoproterenol or other catecholamines. Pulmonary vascular resistance may decrease if it is elevated initially and mean pulmonary artery pressure may decrease or remain unchanged. Dobutamine does not seem to affect dopaminergic receptors and causes no renal or mesenteric vasodilation; however, urine flow may increase because of increased cardiac output.

Paediatric population
Dobutamine also exhibits inotropic effects in children, but the haemodynamic response is somewhat different than that in adults. Although cardiac output increases in children, there is a tendency for systemic vascular resistance and ventricular filling pressure to decrease less and for the heart rate and arterial blood pressure to increase more in children than in adults.

Pulmonary wedge pressure may increase during infusion of dobutamine in children 12 months of age or younger.

Increases in cardiac output seems to begin at iv infusion rates as low as 1.0 micrograms/kg/minute, increases in systolic blood pressure at 2.5 micrograms/kg/minute, and heart rate changes at 5.5 micrograms/kg/minute.

The increase of dobutamine infusion rates from 10 to 20 micrograms/kg/minute usually results in further increases in cardiac output.

5.2 Pharmacokinetic properties

Absorption: Orally administered dobutamine is rapidly metabolised in the GI tract. Following IV administration, the onset of action of dobutamine occurs within 2 minutes. Peak plasma concentrations of the drug and peak effects occur within 10 minutes after initiation of an IV infusion. The effects of the drug cease shortly after discontinuing an infusion.

Distribution: It is not known if dobutamine crosses the placenta or is distributed into milk.

Elimination: The plasma half-life of dobutamine is about 2 minutes. Dobutamine is metabolised in the liver and other tissues by catechol-O-methyltransferase to an inactive compound, 3-O-methyldobutamine, and by conjugation with glucuronic acid. Conjugates of dobutamine and 3-O-methyldobutamine are excreted mainly in urine and to a minor extent in faeces.

Paediatric population
In most paediatric patients, there is a log-linear relationship between plasma dobutamine concentration and hemodynamic response that is consistent with a threshold model.
Dobutamine clearance is consistent with first-order kinetics over the dosage range of 0.5 to 20 micrograms/kg/minute. Plasma dobutamine concentration can vary as much as two-fold between paediatric patients at the same infusion rate and there is a wide variability in both the plasma dobutamine concentration necessary to initiate a hemodynamic response and the rate of hemodynamic response to increasing plasma concentrations. Therefore, in clinical situations dobutamine infusion rates must be individually titrated.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to the data already included in other sections of this summary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Water for injections

6.2 Incompatibilities

Dobutamine hydrochloride has been reported to be incompatible with alkaline solutions and should not be mixed with sodium bicarbonate 5%, or other strong alkaline solutions i.e. aminophylline, furosemide. Precipitation has occurred with bumetanide, calcium gluconate, insulin, diazepam and phenytoin. Because of the potential physical incompatibilities, dobutamine hydrochloride should not be mixed with other drugs in the same solution.

Dobutamine should not be used with drugs or diluents containing bisulphites or ethanol.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Prior to first use, do not store above 25°C.

Infusions must be aseptically prepared.

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C.

Discard any unused product.

Solutions of dobutamine hydrochloride may have a pink discolouration. This discolouration, which will increase with time, results from a slight oxidation of the drug. However, there is no significant loss of drug potency within the recommended maximum in-use storage time of 24 hours at 2^{o}C - 8^{o}C.

6.5 Nature and contents of container

Clear, Type 1glass vial with rubber stopper, containing 250 mg of dobutamine (as dobutamine hydrochloride). Single vial packs.

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

Dobutamine must be diluted to a final volume of at least 50ml with the following IV infusion solutions:
Sodium Chloride Intravenous Infusion BP
5% Dextrose Intravenous Infusion BP

If diluting to 250ml, 500ml or 1000 ml, dilution will give a concentration for administration as follows:
250ml contains 1000 micrograms/ml of dobutamine.
500ml contains 500 micrograms/ml of dobutamine.
1000ml contains 250 micrograms/ml of dobutamine.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0437/036/001

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10 DATE OF REVISION OF THE TEXT

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