SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dobutamine 12.5mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dobutamine Hydrochloride 14.01 mg/ml equivalent to dobutamine 12.5mg/ml.

Each 12.5mg of dobutamine sterile concentrate contains 0.06 mg of sodium.

Excipients with known effect; sodium metabisulfite (E223)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

4.1 Therapeutic indications

Dobutamine is indicated in adults as inotropic support in the short term treatment of conditions characterised by low output cardiac failure, e.g. myocardial infarction, open heart surgery, cardiomyopathies, septic shock and cardiogenic shock. It can also increase or maintain cardiac output during positive end expiratory pressure (PEEP) ventilation.

Paediatric population

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 is administered by continuous intravenous infusion due to the short half life of dobutamine. The solution must first be diluted to at least 50ml in an iv container with one of the following intravenous solutions:

Sodium Chloride Intravenous Infusion BP
5% Glucose Intravenous Infusion BP
5% Glucose + 0.9% Sodium Chloride Intravenous Infusion BP

5% Glucose + 0.45% Sodium Chloride Intravenous Infusion BP
Sodium Lactate Intravenous Infusion BP

20ml Dobutamine Sterile Concentrate will yield the following concentrations when diluted:

In 250ml: 1000 micrograms/ml of dobutamine
In 500ml: 500 micrograms/ml of dobutamine
In 50ml: 5,000 micrograms/ml (only appropriate in patients on restricted fluid intake, for administration by infusion pump for accuracy of dosing).

The prepared solution should be used within 24 hours.

After dilution, dobutamine should be administered intravenously through an, intravenous needle or catheter. An iv drip chamber or other suitable metering device is essential for controlling the rate of flow in drops per minute.

Adults, including the elderly:

Cardiac failure:-

The usual infusion rate is 2.5 to 10 micrograms per kg body weight per minute,m according to the patient's heart rate, blood pressure, urine output, and if available cardiac output. Doses ranging from 0.5 up to 40 micrograms per kg body weight per minute have been used.

It is recommended that treatment with dobutamine should be discontinued gradually.

<u>Paediatric population</u>

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 a 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 1mg/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 30mg/kg body weight to a final volume of 50mL of infusion fluid. An intravenous infusion rate of 0.5mL/hour provides a dose of 5 micrograms/kg/minute.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In general, sympathomimetic agents should be used with caution in patients who may be particularly susceptible to their effects, particularly those with hyperthyroidism. Great care is also needed in patients with cardiovascular disease such as ischaemic heart disease, acute heart failure, arrhythmia or tachycardia, occlusive vascular disorders including arteriosclerosis, hypertension or aneurysms. Anginal pain may be precipitated in patients with ischaemic heart disease, particularly after myocardial infarction. Care is also required when sympathomimetic agents are given to patients with diabetes mellitus or closed angle glaucoma.

Avoid the use of sympathomimetic agents in patients with phaeochromocytoma.

In particular, dobutamine should be avoided or used only with great caution in patients with marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis. It may exacerbate pre-existing tachycardia and hypertension. Metabolic acidosis, hypoxia, hypercapnia and hypovolaemia should be corrected before and during dobutamine treatment. Use with caution in cardiogenic shock complicated by severe hypotension.

If an undue increase in heart rate or systolic blood pressure occurs during administration of dobutamine, or an arrhythmia is precipitated, the dose should be reduced or interrupted.

Stress cardiomyopathy (Takotsubo syndrome) is a possible severe complication of the use of dobutamine during stress echocardiography (see section 4.8). The administration of dobutamine for stress echocardiography should be only undertaken by a physician experienced with the procedure. The physician should be vigilant during the test and the recovery period and be prepared for appropriate therapeutic intervention during the test. In the event

of stress cardiomyopathy (Takotsubo syndrome) dobutamine should be stopped immediately.

Special care should be taken with the use of dobutamine in the elderly.

Tolerance may occur with continuous infusions of dobutamine over more than 72 hours.

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.

Important information about the sodium content of Dobutamine Sterile Concentrate
This medicinal product contains less than 1mmol sodium (23mg) per dose, i.e. essentially 'sodium-free'.

Dobutamine Sterile Concentrate contains sodium metabisulfite (E223)
Dobutamine Sterile Concentrate contains sodium metabisulfite (E223) which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interactions

Alpha-blockers: Potential for hypotension and tachycardia to occur with concomitant administration of sympathomimetics and alpha-blockers such as phenoxybenzamine.

Anaesthetics: Although it is less likely than adrenaline to produce ventricular arrhythmias, dobutamine should be used with extreme caution during anaesthesia with cyclopropane, halothane and other halogenated anaesthetics.

Anti-arrhythmics: An increased risk of arrhythmias may occur if sympathomimetic agents are given to patients receiving quinidine.

Antidepressants: Hypertension and an increased risk of arrhythmias may occur if sympathomimetic agents are given to patients receiving tricyclic antidepressants. Many sympathomimetics interact with MAOIs (possibility of

hypertensive crisis), and should not be given to patients receiving such treatment or within 14 days of its termination.

Antihypertensives: Special care is advisable in patients receiving antihypertensive therapy in whom dobutamine may increase blood pressure.

Beta-blockers: The inotropic effects of dobutamine on the heart are reversed by concomitant administration of beta-blockers. Dobutamine may be ineffective or may have a slight vasoconstricting effect in patients who have recently received beta-blockers. There is a possibility of severe hypertension and bradycardia occurring with concurrent use of dobutamine and beta-blockers, especially non-selective beta-blockers.

Calcium Chloride: Calcium chloride infusion may reduce the cardiotonic effects of dobutamine.

Cardiac Glycosides: An increased risk of arrhythmias may occur if sympathomimetic agents are given to patients receiving cardiac glycosides.

Cimetidine: It is possible that cimetidine may inhibit the uptake and/or the metabolism of dobutamine by the liver with a subsequent increase in the degree and duration of its action.

Doxapram: An increased risk of hypertension with concomitant use of the sympathomimetic agents and doxapram.

Entacapone: The effects of dobutamine may be enhanced by concomitant administration of entacapone.

Ergot Alkaloids: Potential for ergotism to occur with concomitant administration of sympathomimetics and ergotamine or egometrine (ergonovine) or methysergide. There is a possibility of ergotamine or egometrine (ergonovine) enhancing the pressor effect and severe hypertension occurring.

Oxytocin: There is a possibility of oxytocin enhancing the pressor effects of sympathomimetics with or without hypertension.

Rasagiline: Avoid concomitant use of sympathomimetics with rasagiline.

4.6 Fertility, pregnancy and lactation

Studies in rats and rabbits have revealed no evidence of a teratogenic effect of dobutamine. There are no adequate studies in human pregnancy and therefore dobutamine should not be used without very careful consideration of the balance of risk.

It is not known whether this drug is excreted in human milk, so caution should be exercised. If a mother requires dobutamine treatment, breast feeding should be discontinued for the duration of treatment.

4.7 Effects on ability to drive and use machines

Patients should not drive or operate machinery if experiencing any ill effects.

4.8 Undesirable effects

Effects on the cardiovascular system are complex. Stimulation of alpha-adrenergic receptors produces vasoconstriction with resultant hypertension. Dobutamine may cause a marked increase in heart rate or blood pressure. Hypertensive patients can develop marked systolic hypertension. The rise in blood pressure may produce cerebral haemorrhage and pulmonary oedema. There may also be a reflex bradycardia but stimulation of β_1-adrenergic receptors of the heart may cause tachycardia, palpitations, ectopic heart beats and cardiac arrhythmias, anginal pain and cardiac arrest.

Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation may be at risk of developing a rapid ventricular response. If rapid ventricular rates occur in the presence of obstructive coronary artery disease, myocardial ischaemia may be induced or exacerbated.

Occasionally hypotension with dizziness and fainting and flushing may occur due to vasodilation, and, as with other catecholamines, serum potassium could be reduced.

Other side effects include nausea, vomiting, headache, anxiety, paraesthesias, non-specific chest pain, eosinophilic myocarditis, shortness of breath, myocardial infarction, coronary artery spasm and reactions suggestive of hypersensitivity including rash, fever, eosinophilia, bronchospasm and local cellulitis at the site of infusion. Pruritus of the scalp has been reported. Extravasation of parenterally administered catecholamines may result in tissue necrosis and sloughing. Phlebitis has occasionally been reported at the site of infusion. Partial tolerance may develop with infusions over more than 72 hours, requiring dosage increase. There is the potential for psychosis to occur as a rare side effect of dobutamine. There is also the potential for urinary urgency to occur during infusion of relatively high doses (15 micrograms/kg/minute) of dobutamine.

Side effects with unknown frequency include stress cadiomyopathy (Takotsubo syndrome) (see section 4.4)

<u>Paediatric population</u>

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow card in the Google Play or Apple App Store.

4.9 Overdose

a) Symptoms

Nausea, vomiting, anxiety, palpitations, headache, shortness of breath and anginal and non-specific chest pain. Urinary incontinence has been reported.

Hypertension (which may be systolic and severe), tachyarrhythmias, myocardial ischaemia and ventricular fibrillation due to positive inotropic and chronotropic effects and hypotension resulting from vasodilation.

b) Treatment

Since the half-life of dobutamine is only about two minutes most adverse effects can be corrected by discontinuing or reducing the rate of infusion.
If reduction in the rate of administration or discontinuation of therapy fails to lower the blood pressure, a short-acting alpha-adrenergic blocking agent may be administered.

The patient's condition should be monitored and any appropriate resuscitative measures initiated promptly.

Consider esmolol, metoprolol, or other beta-adrenergic blocking agent for cardiac dysrhythmias.

5.1 Pharmacodynamic properties

Dobutamine is a selective β_1-adrenergic agonist which directly stimulates β_1-adrenergic receptors. Dobutamine also has mild β_2-and α_1-adrenergic receptor agonist effects at therapeutic doses but the main effect is cardiac stimulation (the β_2- and α_1- adrenergic receptor effects are balanced resulting in minimal net direct effect on systemic vasculature.

The β_1-adrenergic effects of dobutamine exert a positive inotropic effect on the myocardium, resulting in increased myocardial contractility, stroke volume and cardiac output. In patients with congestive heart failure, increased left ventricular filling pressure decreases. Dobutamine, in therapeutic doses, causes a decrease in peripheral resistance but because of augmented cardiac output, systolic blood pressure and pulse pressure will be unchanged or

increased. Heart rate is usually not substantially changed but coronary blood flow and myocardial oxygen consumption are usually increased.

Dobutamine facilitates atrioventricular conduction. The tendency to induce cardiac arrhythmias may be slightly less than that of dopamine (and considerably less than isoproterenol or other catecholamines). Dobutamine does not affect dopaminergic receptors (unlike dopamine) and causes no renal or mesenteric vasodilation, but urine flow may increase due to 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

Dobutamine is virtually inactive after oral administration because of extensive presystemic metabolism in the gastrointestinal mucosa and liver, so it is administered by intravenous infusion. The onset of action after intravenous administration is rapid (about 2 minutes) and the peak effect occurs within 10 minutes. The mean plasma half life in patients with heart failure is 2.4 minutes. The duration of action is less than 10 minutes.

In patients with low output cardiac failure, dobutamine has a mean volume of distribution of $0.20 \pm 0.08 Lkg^{-1}$ and a clearance of ~ 59 mL min^{-1} kg^{-1}. The extent to which dobutamine crosses the placenta is not known nor is it known if it is distributed into milk.

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 pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite
Water for injections
3M Hydrochloric acid
3M Sodium hydroxide

6.2 Incompatibilities

Because of potential physical incompatibilities, it is recommended that dobutamine not be mixed with other drugs in the same solution.

Do not add dobutamine to 5% sodium bicarbonate intravenous infusion or to any other strongly alkaline solutions.

Dobutamine hydrochloride should not be used in conjunction with other agents or diluents containing both sodium bisulfite and ethanol.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light.

Store below 25°C.

If not required immediately, the diluted solution may be stored for up to 24 hours in a refrigerator. Solutions of dobutamine may turn pink over time due to slight oxidation. This does not affect the potency of the product.

6.5 Nature and contents of container

Neutral glass ampoules containing 5ml, 10ml or 20ml of solution The ampoules are packed into cartons containing 1, 5 or 10 ampoules.

6.6 Special precautions for disposal

Refer to Section 4.2

7 MARKETING AUTHORISATION HOLDER

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LL13 9UF

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8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0075

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