

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dobutamine 12.5mg/ml Sterile Concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20ml solution contains Dobutamine Hydrochloride equivalent to 250mg dobutamine.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless or almost colourless sterile aqueous solution intended for intravenous infusion to human beings after dilution with a suitable diluent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Dobutamine may also be used as an alternative to exercise for cardiac stress testing in patients for whom exercise testing is impracticable. This use of dobutamine should be confined to units where exercise stress testing is routinely performed and the usual monitoring and precautions required for such testing should be applied when Dobutamine is used for this purpose.

4.2 Posology and method of administration

Dobutamine Concentrate must be further diluted to at least 50ml prior to administration in an i.v. container with one of the intravenous solutions listed below:

Sodium Chloride Intravenous Infusion BP

5% Dextrose Intravenous Infusion BP

5% Dextrose + 0.9% Sodium Chloride Intravenous Infusion BP

5% Dextrose + 0.45% Sodium Chloride Intravenous Infusion BP

Sodium Lactate Intravenous Infusion BP

For example, diluting to 250 or 500ml will provide the following concentrations for administration:

250ml contains 1,000 micrograms/ml of dobutamine

500ml contains 500 micrograms/ml of dobutamine

The prepared solution should be used within 24 hours

Administration: Because of its short half-life, Dobutamine is administered as a continuous intravenous infusion. After dilution, it should be administered through an intravenous needle or catheter using an i.v. drip chamber or other suitable metering device to control the rate of flow.

Recommended dosage for adults, including the elderly: The usual dose range is 2.5 to 10 micrograms/kg/minute. Occasionally, a dose as low as 0.5 micrograms/kg/minute will produce a response. Rarely, up to 40 micrograms/kg/minute may be required.

The rate of administration and duration of therapy should be adjusted according to the patient's response as determined by heart rate, blood pressure, urine flow and, where possible, measurements of cardiac output.

When discontinuing therapy, a gradual reduction in dosage is generally advised.

Side effects are dose-related and are infrequent with infusion rates below 10 micrograms/kg/minute. Infusion rates of up to 40 micrograms/kg/minute have been used occasionally without significant adverse effects.

The final volume administered should be determined by the fluid requirement of the patient.

Concentrations of up to 5,000 micrograms/ml have been used in patients on restricted fluid intake. To ensure accurate dosage, an infusion pump is required to administer high concentrations of Dobutamine.

Cardiac Stress testing: The recommended dose is an incremental increase of 5 micrograms/kg/minute from 5 up to 20 micrograms/kg/minute, each dose being infused for eight minutes. It is essential to monitor the ECG continuously and to terminate the infusion in the event of >3mm ST segment depression or any ventricular arrhythmia. The infusion should also be stopped if the heart rate reaches the age/sex maximum, systolic BP rises above 220mm Hg or any side effects occur.

Paediatric Use: the safety and efficacy of Dobutamine in children have not been established.

4.3 Contraindications

- Hypersensitivity to dobutamine, sodium metabisulphite or any of the other ingredients.

- Hypovolaemia
- Pheochromocytoma.

4.4 Special warnings and precautions for use

In the event of an undue increase in heart rate or systolic blood pressure, 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 facilitates A-V conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

Particular care is required when administering dobutamine to patients with acute myocardial infarction, as any significant increase in heart rate or excessive increases in arterial pressure that occur may intensify ischaemia and cause anginal pain and ST segment elevation.

Inotropic agents, including dobutamine, do not improve haemodynamics in most patients with mechanical obstruction that hinders either ventricular filling or outflow, or both. Inotropic response may be inadequate in patients with markedly reduced ventricular compliance. Such conditions are present in cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis.

Minimal vasoconstriction has occasionally been observed, most notably in patients recently treated with a β -blocking drug. The inotropic effect of dobutamine results from stimulation of cardiac β_1 receptors and this effect is prevented by β -blocking drugs. However, dobutamine has been shown to counteract the cardiodepressive effects of β -blocking drugs. Conversely, α -adrenergic blockade may make the β_1 and β_2 effects apparent, resulting in tachycardia and vasodilatation.

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

Cardiac rupture is a potential complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) may be influenced by a variety of factors including site of, and time since, infarct. There have been very rare, fatal reports of acute cardiac rupture during dobutamine stress testing. These events have occurred during pre-discharge examination in patients hospitalised with recent (within 4-12 days) myocardial infarction. In the reported cases of free wall rupture, resting echocardiogram showed a dyskinetic and thinned inferior wall. Patients considered at risk of cardiac rupture during dobutamine testing should therefore be carefully evaluated prior to testing.

During the administration of dobutamine concentrate, as with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure, and infusion rate should be monitored closely during administration of dobutamine. When initiating therapy, electrocardiographic monitoring is advisable until a stable response is achieved.

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Dosage reduction or discontinuing the infusion is usually sufficient to restore baseline values, but rarely intervention may be required and reversibility may not be immediate.

Dobutamine concentrate should be used with caution in the presence of severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70mm Hg).

Hypovolaemia should be corrected when necessary with whole blood or plasma before administering dobutamine.

During dobutamine therapy, if arterial blood pressure remains low or decreases progressively, despite adequate ventricular filling pressure and cardiac output, consideration may be given to the concomitant use of a peripheral vasoconstrictor drug, such as dopamine or noradrenaline.

Dobutamine Concentrate contains sodium metabisulphite. Sulphites may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulphite sensitivity is seen more frequently in asthmatic than in non-asthmatic subjects.

Caution should be taken in patient with renal failure (especially being treated for congestive cardiac failure), as myoclonus has been reported as an adverse effect of this product in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

Halogenated anaesthetics:

Although it is less likely than adrenaline to cause ventricular arrhythmias, dobutamine concentrate should be used with great caution during anaesthesia with cyclopropane, halothane and other halogenated anaesthetics.

Entacapone:

The effects of Dobutamine concentrate may be enhanced by entacapone.

Beta-blockers:

The inotropic effect of dobutamine stems from stimulation of cardiac beta1 receptors, this effect is reversed by concomitant administration of beta-blockers. Dobutamine has been shown to counteract the effect of beta-blocking drugs. In therapeutic doses, dobutamine has mild alpha1- and beta2-agonist properties. Concurrent administration of a non-selective beta-blocker such as propranolol can result in elevated blood pressure, due to alpha-mediated vasoconstriction, and reflex bradycardia. Beta-blockers that also have alpha-blocking effects, such as carvedilol, may cause hypotension during concomitant use of dobutamine due to vasodilation caused by beta2 predominance (see section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation

Reproduction studies in rats and rabbit have revealed no evidence of impaired fertility, harm to the foetus or teratogenic effects due to Dobutamine. As there are no adequate and well controlled studies in pregnant women and as animal

reproduction studies are not always predictive of human response, Dobutamine should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.

As it is not known whether Dobutamine is excreted in breast milk, breast-feeding should be suspended for the duration of treatment.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

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 concentrate for 72 hours or more; therefore, higher doses may be required to maintain the same effects.

Immune system disorders:

Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to sulphite sensitivity (see section 4.4 Special warnings and other precautions for use).

Metabolism and nutrition disorders:

As with other catecholamines, decreases in serum potassium concentrations have occurred. Consideration should be given to monitoring serum potassium.

Cardiac disorders:

Increased heart rate, palpitations, angina pectoris, chest pain, ectopic heart beats, arrhythmia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, myocardial ischaemia, coronary artery spasm, electrocardiogram ST segment elevation, myocardial infarction.

Left ventricular outflow tract obstruction has been reported during dobutamine stress echocardiography.

There have been very rare reports of fatal cardiac rupture during dobutamine stress testing (see section 4.4).

Eosinophilic myocarditis has been noted in explanted hearts of patients who had undergone treatment with multiple medications including dobutamine or other inotropic agents prior to transplantation.

Vascular disorders:

Hypertension. Marked increase in systolic blood pressure indicates overdose (see also section 4.5 Interactions).

Hypotension (see sections 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interactions).

Nervous system disorders:

Myoclonus has been reported in patients with severe renal failure receiving dobutamine.

Respiratory, thoracic and mediastinal disorders:

Shortness of breath, bronchospasm, asthma (see Immune system disorders)

General/Other disorders:

Non-specific chest pain, headache, nausea.

Reactions at the site of intravenous infusion: Phlebitis has occasionally been reported and local inflammatory changes have been described following inadvertent infiltration. Very rare cases of cutaneous necrosis have been reported.

4.9 Overdose

Overdose of Dobutamine have been reported rarely. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath 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 vasodilatation.

The duration of action of Dobutamine hydrochloride is generally short (half-life, approximately 2 minutes). Dobutamine infusion should be temporarily discontinued until the patient's condition stabilises. The patient should be monitored and any appropriate resuscitative measures initiated promptly.

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 synthetic sympathomimetic agent. It is a direct-acting and the primary mode of action of Dobutamine is to increase cardiac contractility by stimulating the β_1 receptors of the heart.

5.2 Pharmacokinetic properties

Dobutamine is inactive when given by mouth. It is rapidly inactivated in the body and the routes of metabolism include methylation and conjugation. The

plasma half-life of Dobutamine is about 2 minutes. Metabolites of Dobutamine are excreted mainly by the kidneys.

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 Metabisulphite
Hydrochloric Acid 10% w/v
Sodium Hydroxide 10% w/v q.s
Water for Injections

6.2 Incompatibilities

Do not add Dobutamine Concentrate to 5% Sodium Bicarbonate Intravenous Infusion BP or to any other strongly alkaline solutions. Because of potential physical incompatibilities, it is recommended that Dobutamine hydrochloride not be mixed with other drugs in the same solution.

Dobutamine Concentrate should not be used with other agents or other diluents containing both sodium metabisulphite and ethanol. Solutions containing Dobutamine Hydrochloride may turn pink; the colour may intensify with time. This colour change is due to slight oxidation of the drug, but there is no significant loss of potency during the recommended storage period.

6.3 Shelf life

2 years.

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 reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

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

20ml clear One point cut (OPC) glass ampoules, glass type 1. Ph.Eur
Packs of 1, 5 or 10 ampoules

6.6 Instructions for use/handling

The carton label stated the following:
The solution must be diluted before use.
Do not dilute with alkaline solutions.
Dilute to at least 50ml before administration by intravenous infusion.
Use as directed by the physician.
Keep out of reach of children.
If only part used, discard the remaining solution.
Please refer to 4.2 Posology and Method of Administration for details on instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Antigen International Limited
Roscrea
Co Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

PL 02848/0180

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 November 1999

10. DATE OF REVISION OF THE TEXT

11/05/2010