



SUMMARY OF PRODUCT CHARACTERISTICS

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Dobutamine Concentrate 250 mg/20 ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Dobutamine Hydrochloride USP equivalent to Dobutamine 12.5 mg.

3. PHARMACEUTICAL FORM

Sterile Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Dobutamine Concentrate may also be used for cardiac stress testing as an alternative to exercise in patients for whom routine exercise cannot be satisfactorily performed. This use of dobutamine should only be undertaken in units which already perform exercise stress testing and all normal care and precautions required for such testing are also required when using dobutamine for this purpose.

4.2 Posology and method of administration

Route of Administration: For intravenous use only.

Dobutamine Concentrate must be diluted to at least 50 ml prior to administration in an IV 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 ml or 500 ml will provide the following concentrations for administration:

250 ml contains 1,000 micrograms/ml of dobutamine

500 ml contains 500 micrograms/ml of dobutamine

The prepared solution should be used within 24 hours.

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

Recommended dosage for adults and the elderly: The usual dose 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 the duration of therapy should be adjusted according to the patient's response as determined by heart rate, blood pressure, urine flow, and if possible, measurement of cardiac output.

It is advisable to reduce the dosage of dobutamine hydrochloride gradually rather than abruptly stopping therapy.

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

The final volume administered should be determined by the fluid requirements of the patient. Concentrations as high as 5,000 micrograms/ml have been used in patients on a restricted fluid intake. High concentrations of dobutamine concentrate should only be given with an infusion pump, to ensure accurate dosage.

Cardiac stress testing: When used as an alternative to exercise for 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 8 minutes. Continuous ECG monitoring is essential and the infusion terminated in the event of > 3 mm ST segment depression or any ventricular arrhythmia. The infusion should also be terminated if heart rate

reaches the age/sex maximum, systolic blood pressure rises above 220 mm Hg or any side effects occur.

Children: The safety and efficacy of dobutamine concentrate therapy in children have not been established.

4.3 Contraindications

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

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 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 stems 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, 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. 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. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to base-line 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 70 mm Hg).

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

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 concomitant use of a peripheral vasoconstrictor agent, 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 non-asthmatic people.

Also the carton text shall contain the following statements:

“Dilute to at least 50 ml volume before intravenous infusion”
“If not required immediately, the diluted solution may be stored for up to 24 hours in a refrigerator.”
“Keep out of the reach of children”
“If only part used, discard the remaining solution”
“Protect from light”
“Do not store above 25 °C”

4.5 Interactions with other medicinal products and other forms of interactions

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 rabbits 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.

4.7 Effects on ability to drive and use machines

Not applicable in view of the indications for use and the short half-life of the drug.

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 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

Overdoses of dobutamine concentrate 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 concentrate is generally short (half-life, approximately 2 minutes). Dobutamine concentrate 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 directly stimulates β -adrenergic receptors and is generally considered a selective β_1 -adrenergic agonist, but the mechanisms of action of the drug are complex. It is believed that the β -adrenergic effects result from stimulation of adenylyl cyclase activity. In therapeutic doses, dobutamine also has mild β_2 - and α_1 - adrenergic receptor agonist effects, which are relatively balanced and result in minimal net direct effect on systemic vasculature. Unlike dopamine, 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 β_1 -adrenergic stimulation, experimental evidence suggests that

α_1 -adrenergic stimulation may also be involved and that the α_1 -adrenergic activity results mainly from the (-) -stereoisomer of the drug.

The β_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 in healthy individuals and in patients with congestive heart failure. 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.

Electrophysiologic studies have shown that dobutamine facilitates atrio-ventricular 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. Unlike dopamine, dobutamine does not seem to affect dopaminergic receptors and causes no renal or mesenteric vasodilatation; however, urine flow may increase because of increased 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.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Products Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Metabisulphite BP
Sodium Hydroxide EP
Hydrochloric Acid EP
Water for Injections EP
Carbon Dioxide HSE

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 injections should not be used with other agents or diluents containing both sodium metabisulphite and ethanol.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Protect from light, do not store above 25°C.

6.5 Nature and contents of container

20 ml clear glass ampoule. Packed in cardboard cartons to contain 1, 5 or 10 ampoules x 20 ml.

6.6 Instructions for use, handling and disposal

Use as directed by a physician.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Hameln pharmaceuticals
Gloucester
UK

8. MARKETING AUTHORISATION NUMBER

PL 01502/0054

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

16th December 1994

10. DATE OF (PARTIAL) REVISION OF TEXT

09/02/10