1 PRODUCT NAME

Dobutamine-hameln 12.5 mg/ml concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains dobutamine hydrochloride equivalent to dobutamine 12.5 mg.
Each ampoule contains 250 mg dobutamine in 20 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dobutamine is indicated when inotropic support is necessary for the treatment of patients with hypoperfusion states in whom cardiac output is insufficient to meet circulatory demands.

Dobutamine is also indicated when inotropic support is required for the treatment of patients in whom abnormally increased ventricular filling pressures introduce the risk of pulmonary congestion and oedema. Conditions which may precipitate such situations include the following hypoperfusion states:

Initially cardiac in origin

A. Acute heart failure

1. Acute myocardial infarction
2. Cardiogenic shock
3. Following cardiac surgery
4. Medicine-induced depression of cardiac contractility such as that which occurs in excessive β-adrenergic receptor blockade.

B. Chronic heart failure

1. Acute decompensation of chronic congestive heart failure
2. Temporary inotropic support in advanced chronic congestive heart failure, as an adjunct to therapy with conventional oral inotropic agents, systemic vasodilators, and diuretics.

Initially noncardiac in origin

1. Acute hypoperfusion states secondary to trauma, surgery, sepsis, or hypovolaemia when mean arterial pressure is above 70-mm Hg and pulmonary capillary wedge pressure is 18-mm Hg or greater, with inadequate response to volume repletion and increased ventricular filling pressure
2. Low cardiac output secondary to mechanical ventilation with positive end-expiratory pressure (PEEP).

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.

Dobutamine stress echocardiography
Dobutamine hydrochloride may be used as a substitute for physical exercise in stress testing in the diagnosis of coronary artery disease. When dobutamine hydrochloride is used for this purpose, as is the case when exercise is used for stress testing, patients should be informed of the potential risks involved in the test. In addition, patients should be subjected to the same close monitoring that is mandatory in standard exercise stress tests, including continuous electrocardiographic monitoring.

4.2 Dose and method of administration

Administration
Because of its short half-life, dobutamine hydrochloride must be administered as a continuous intravenous infusion. Following the initiation of a constant rate infusion, or upon changing the rate, a steady-state dobutamine plasma concentration is achieved within approximately 10 minutes. Thus, loading doses or bolus injections are not necessary and are not recommended.

Dobutamine must be diluted prior to use.

Recommended Dosage

Dosage in Adults
The rate of infusion needed to increase cardiac output has ranged from 2.5 to 10 mcg/kg/min in the majority of patients. Frequently, doses up to 20 mcg/kg/min are required for adequate haemodynamic improvement. On rare occasions, infusion rates up to 40 mcg/kg/min have been reported.

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by the following clinical indicators: haemodynamic parameters such as heart rate and rhythm, arterial pressure, and, whenever possible, cardiac output and measurements of ventricular filling pressures (central venous, pulmonary capillary wedge, and left atrial), and signs of pulmonary congestion and organ perfusion (urine flow, skin temperature, and mental status).

Concentrations up to 5,000 mg/L have been administered to humans (250 mg/50 mL). The final volume administered should be determined by the fluid requirements of the patient.

Rather than abruptly discontinuing therapy with dobutamine hydrochloride, it is often advisable to decrease the dosage gradually.

Dosage in paediatric patients
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 haemodynamic 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.

Dobutamine stress echocardiography

Administration in stress echocardiography is undertaken by gradually increasing dobutamine infusion.

The most frequently applied dosage scheme starts with 5 µg/kg/min dobutamine increased every 3 minutes to 10, 20, 30, 40 µg/kg/min until a diagnostic endpoint is reached.

If no endpoint is reached atropine sulphate may be administered at 0.5 to 2 mg in divided doses of 0.25-0.5 mg at 1 minute intervals to increase the heart rate. Alternatively, the infusion rate of dobutamine may be increased to 50 µg/kg/min.

Dosage Units

Most reports on dobutamine hydrochloride have expressed the dose in relation to body mass, for example, mcg/kg/min. This practice is useful to relate doses in infants and children to those in adults. Among adults, body mass has little influence on the effect of dobutamine hydrochloride; since the dosage of dobutamine hydrochloride should be titrated in each patient, adults may be as easily dosed with mcg/min units. The dosage of dobutamine hydrochloride may be initiated at 100 to 200 mcg/min and increased gradually to 1,000 to 2,000 mcg/min or greater, depending on the clinical and haemodynamic response of the individual patient.

Rates of Infusion Based on Concentration of Dobutamine Hydrochloride

The rates of fluid infusion that are required to deliver specific dosages are a function of the concentration of dobutamine hydrochloride in the infusate. The following table provides a guideline of infusion rates (mL/kg/min) required for 3 frequently used concentrations of dobutamine hydrochloride (250, 500, and 1,000 mg/L) in order to deliver the medicine dosages (mcg/kg/min) which are indicated in the left hand column of the table.

Rates of infusion for concentrations of 250, 500 and 1000 µg/mL:

Medicine Delivery Rate (mcg/kg/min)	**Infusion Delivery Rate**		
	250 mg/L * (mL/kg/min)	500 mg/L ** (mL/kg/min)	1000 mg/L *** (mL/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.010	0.0050
7.5	0.03	0.015	0.0075
10	0.04	0.020	0.0100
12.5	0.05	0.025	0.0125
15	0.06	0.030	0.0150

*250 mg/L of diluent

**500 mg/L or 250 mg/500 mL of diluent

***1000 mg/L or 250 mg/250 mL of diluent

Prior to administration the concentrate for solution for infusion must be diluted to a volume of 50 mL or more. In case of dilution the solution for infusion should be diluted immediately before use. For dilution, a compatible infusion solution should be used. Chemical and physical compatibility have been demonstrated with a number of diluent solutions including 5% glucose solution, 0.9% sodium chloride solution and 0.45% sodium chloride in 5 % glucose solution for 24 hours at room temperature in glass containers without special protection from light. Full information as to suitable diluents is provided in section 6.3.

Paediatric patients: For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5 mg/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.

Dobutamine stress echocardiography: For detection of myocardial ischaemia and of viable myocardium dobutamine may only be administered by a physician with sufficient experience in conducting cardiology stress tests. Continuous monitoring of all wall areas via echocardiography, and ECG as well as control of blood pressure is necessary.

Monitoring devices as well as emergency medicines must be available (e.g. defibrillator, I.V. beta-blockers, nitrates, etc.) and staff trained in the resuscitation procedure must be present.

4.3 Contraindications

Previous manifestations of hypersensitivity to dobutamine or any of the excipients.

Dobutamine must not be used in the case of:
- known hypersensitivity to dobutamine or to any of the excipients,
- mechanical obstruction of ventricular filling and/or of outflow, such as pericardial tamponade, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, severe aortic stenosis,
- hypovolaemic conditions.
- Phaeochromocytoma.

Dobutamine stress echocardiography

Dobutamine must not be used for detection of myocardial ischaemia and of viable myocardium in case of:
- recent myocardial infarction (within the last 30 days),
- unstable angina pectoris,
- stenosis of the main left coronary artery,
- haemodynamically significant outflow obstruction of the left ventricle including hypertrophic obstructive cardiomyopathy,
- haemodynamically significant cardiac valvular defect,
- severe heart failure (NYHA III or IV),
- predisposition for or documented medical history of clinically significant or chronic arrhythmia, particularly recurrent persistent ventricular tachycardia,

- significant disturbance in conduction,
- acute pericarditis, myocarditis or endocarditis,
- aortic dissection,
- aortic aneurysm,
- poor sonographic imaging conditions,
- inadequately treated / controlled arterial hypertension,
- obstruction of ventricular filling (constrictive pericarditis, pericardial tamponade),
- hypovolaemia,
- previous experience of hypersensitivity to dobutamine.

Note:
If administering atropine, the respective contraindications have to be observed.

4.4 Special warnings and precautions for use

Adult population

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.

Dobutamine stress echocardiography

Because of possible life-threatening complications, the administration of dobutamine for stress echocardiography should only be undertaken by a physician with sufficient personal experience of the use of dobutamine for this indication.

The use of Dobutamine 12.5 mg/ml concentrate for solution for infusion 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 (see *section 4.3*)

Cardiac rupture is a potential complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) maybe 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.

Dobutamine stress echocardiography must be discontinued if one of the following diagnostic endpoints occurs:

- reaching the age-predicted maximal heart rate [(220-age in years) x 0.85]
- systolic blood pressure decrease greater than 20 mmHg
- blood pressure increase above 220/120 mmHg
- progressive symptoms (angina pectoris, dyspnoea, dizziness, ataxia)
- progressive arrhythmia (e.g. coupling, ventricular salvos)
- progressive conduction disturbances
- recently developed wall motility disorders in more than 1 wall segment (16-segment model)
- increase of endsystolic volume
- development of repolarisation abnormality (due to ischaemia horizontal or down sloping ST segment depression more than 0.2 mV at an interval of 80 (60) ms after the J point compared to baseline, progressive or monophasic ST segment elevation above 0.1 mV in patients without a previous myocardial infarction
- reaching peak dose

In the event of serious complications (see section 4.8) dobutamine stress echocardiography must be stopped immediately.

During the administration of Dobutamine 12.5 mg/ml concentrate for solution for infusion, 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 12.5 mg/ml concentrate for solution for infusion 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 12.5 mg/ml concentrate for solution for infusion contains sodium metabisulfite. Sulfites may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

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 medicines and other forms of interaction

Halogenated anaesthetics:

Although it is less likely than adrenaline to cause ventricular arrhythmias, Dobutamine 12.5 mg/ml concentrate for solution for infusion should be used with great caution during anaesthesia with cycloproprane, halothane and other halogenated anaesthetics.

Entacapone*:*

The effects of Dobutamine 12.5 mg/ml concentrate for solution for infusion may be enhanced by entacapone.

Beta-blockers:

The inotropic effect of dobutamine stems from stimulation of cardiac $beta_1$ 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 $alpha_1$- and $beta_2$-agonist properties. Concurrent administration of anon-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 $beta_2$ predominance (see section *4.4 Special warnings and precautions for use*).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2

Reproduction studies performed in rats at doses up to 3.5 times the normal human dose (10 mcg/kg/min for 24 h, total daily dose of 14.4 mg/kg) and in rabbits at doses up to 2 times the normal human dose have revealed no evidence of harm to the foetus or teratogenic effects due to dobutamine hydrochloride. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, dobutamine hydrochloride should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.

Breast-feeding

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when dobutamine hydrochloride is administered to a nursing woman. If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

Fertility

No data are available.

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

Adult population

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 12.5 mg/ml concentrate for solution for infusion for 72 hours or more; therefore, higher doses may be required to maintain the same effects.

Evaluation of undesirable effects is based on the following frequency scale:

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
Not known:	cannot be estimated from the available data.

<u>Immune system disorders:</u>	
Not Known:	Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to sulfite sensitivity (see section *4.4 Special warnings and other precautions for use*).
<u>Blood and lymphatic system disorders</u>	
Common:	Eosinophilia, inhibition of thrombocyte aggregation (only when continuing infusion over a number of days)
<u>Metabolism and nutrition disorders</u>	
Very rare:	Hypokalaemia
<u>Nervous system disorders</u>	
Common:	Headache
Not known:	Paraesthesia, tremor, myoclonic spasm. Myoclonus has been reported in patients with severe renal failure receiving dobutamine
<u>Cardiac disorders / vascular disorders</u>	
Very common:	Increase of the heart rate by ≥ 30 beats/min
Common:	Blood pressure increase of ≥ 50 mmHg. Patients suffering from arterial hypertension are more likely to have a higher blood pressure increase. Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles. Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised prior to dobutamine infusion. Vasoconstriction in particular in patients who have previously been treated with beta receptor blockers. Anginal pain, palpitations

Uncommon:	Ventricular tachycardia, ventricular fibrillation
Very rare:	Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest
Not known:	Electrocardiogram ST segment elevation Decrease in pulmonary capillary pressure 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. Children: pronounced increase of heart rate and/or blood pressure as well as a lower decrease of the pulmonary capillary pressure than adults. Increase of pulmonary capillary pressure in children under1.
Gastrointestinal disorders	
Not known:	Nausea
Psychiatric disorders	
Not known:	Restlessness, feeling of heat and anxiety
Renal and urinary disorders	
Not known:	Urinary urgency

Dobutamine stress echocardiography

Cardiac disorders / vascular disorders	
Very common:	Pectoral anginal discomfort, ventricular extra-systoles with a frequency of > 6/min
Common:	Supraventricular extrasystoles, ventricular tachycardia
Uncommon:	Ventricular fibrillation, myocardial infarction
Very rare:	Occurrence of a second degree atrioventricular block, coronary vasospasms. Hypertensive/hypotensive blood pressure decompensation, occurrence of an intracavitary pressure gradient, palpitations
Not known:	Stress cardiomyopathy Left ventricular outflow tract obstruction Fatal cardiac rupture
Respiratory system, thoracic and mediastinal disorders	
Common:	Bronchospasm, shortness of breath
Gastrointestinal disorders	
Common:	Nausea
Skin and subcutaneous tissue disorders	
Common:	Exanthema
Very rare:	Petechial bleeding
Musculoskeletal and connective tissue disorders	
Common:	Chest pain
Renal and urinary disorders	
Common:	Increased urgency at high dosages of infusion
General disorders and administration site conditions	
Common:	Fever, phlebitis at the injection site

	In case of accidental paravenous infiltration, local inflammation may develop.
Very rare:	Cutaneous necrosis

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.

Signs and Symptoms
Toxicity from dobutamine hydrochloride is usually due to excessive cardiac β-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short (T½= 2 minutes) because it is rapidly metabolised by catechol-*o*-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, and anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of dobutamine on the myocardium may cause hypertension, tachyarrhythmias, myocardial ischaemia, and ventricular fibrillation. Hypotension may result from vasodilation. If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract.

Treatment
In managing overdosage, consider the possibility of multiple medicine overdoses, interaction among medicines, and unusual medicine kinetics in your patient.

The initial actions to be taken in a dobutamine hydrochloride overdose are discontinuing administration, establishing an airway, and ensuring oxygenation and ventilation. Resuscitative measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lidocaine. Hypertension usually responds to a reduction in dose or discontinuation of therapy.

Protect the patient's airway and support ventilation and perfusion. If needed, meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of medicines from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some medicines that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.

Dobutamine stress echocardiography
If applying one of the common dosage schemes, toxic doses are not reached, not even cumulatively. In case of severe complications during diagnostic administration of dobutamine, the infusion must be

terminated at once and sufficient oxygen supply and ventilation must be guaranteed. Treatment of angina pectoris should be performed with an intravenous beta-blocker with a very short-acting effect. Angina pectoris may also be treated with a sublingually administered nitrate, if necessary. Class I and III antiarrhythmics must not be administrated

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical group C01CA07

Dobutamine hydrochloride is a direct acting inotropic agent whose primary activity results from stimulation of cardiac adrenergic receptors; it produces comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilator effects. In contrast with dopamine, it does not release norepinephrine and its actions are not dependent on norepinephrine stores in the heart.

In animal studies, dobutamine hydrochloride produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In humans, dobutamine hydrochloride increases stroke volume and cardiac output and decreases ventricular filling pressure and total systemic and pulmonary vascular resistances. The ventricular function curve is shifted upwards and to the left as a reflection of increased myocardial contractility.

Heart rate is not increased significantly by the usual dosage of dobutamine hydrochloride; however, significant tachycardia may occur with high doses (usually greater than 10 mcg/kg/min).

Arterial blood pressure usually is not changed significantly by dobutamine hydrochloride because the effect of the increase in cardiac output is balanced by the concomitant decrease in peripheral vascular resistance. Both increments and decrements in arterial blood pressure have been reported. Patients with pre-existing arterial hypertension, even those who are normotensive at the time, seem more susceptible to sustaining a pressor response.

In animals, dobutamine hydrochloride has been shown to decrease pulmonary hypoxic vasoconstriction. This may result in increased perfusion of poorly ventilated areas. This effect may decrease arterial oxygen saturation in some patients, but to a lesser extent than with dopamine or isoproterenol. Due to the increased cardiac output in such patients, oxygen transport is generally increased by dobutamine hydrochloride. Dobutamine hydrochloride has been shown to prevent or to revert partially the decrease in cardiac output that occurs in patients during mechanical ventilation with positive end-expiratory pressure (PEEP).

Dobutamine hydrochloride does not act at dopamine receptors; thus, it does not selectively dilate renal or splanchnic vessels. Dobutamine hydrochloride may improve renal blood flow, glomerular filtration rate, urine flow, and sodium excretion by increasing cardiac output and by nonselective vasodilatation.

Facilitation of atrioventricular conduction has been observed during administration of dobutamine hydrochloride in human electrophysiologic studies and in patients with atrial fibrillation.

Like all inotropic agents, dobutamine hydrochloride increases myocardial oxygen consumption.

Dobutamine hydrochloride also increases coronary blood flow and myocardial oxygen supply. The changes in oxygen demand are dependent on several factors, including the following: (a) changes in ventricular diameter, which, in turn, determines the level of wall tension required to generate

intraventricular pressure during systole; (b) changes in afterload, generally proportional to changes in systolic blood pressure; and (c) changes in heart rate. When the use of an inotropic agent in a patient with a failing, dilated heart results in a decrease in ventricular diameter, oxygen demand may increase only slightly or not at all, provided afterload and heart rate do not increase markedly. In general, dobutamine hydrochloride does not cause an imbalance between oxygen consumption and supply in either animals or humans with heart disease. Increments in oxygen delivery have often exceeded the augmentation in oxygen uptake during infusion of dobutamine hydrochloride, so that oxygen saturation in coronary sinus blood increases. The arteriovenous extraction ratio of lactic acid, an indirect evidence of unimpeded aerobic metabolism, is generally maintained during administration of dobutamine hydrochloride. In some instances, myocardial lactate extraction has decreased. Net lactate production has been reported in a few patients; this has occurred especially when heart rate and/or arterial blood pressure have increased excessively during infusion of dobutamine hydrochloride, or when ventricular dysfunction was not present prior to the administration of dobutamine hydrochloride.

In patients with angina pectoris who do not have heart failure, infusions of dobutamine hydrochloride have mimicked the effects of physical exercise, increasing myocardial oxygen demand in excess of coronary oxygen supply, and thereby producing reversible clinical signs of myocardial ischaemia. These signs have included anginal pain, ST segment depression, thallium scintigraphic perfusion defects, and new wall motion abnormalities.

Myocardial infarct size and the incidence and severity of ventricular arrhythmias were not increased in patients with acute myocardial infarction who were treated with dobutamine hydrochloride for 24 hours, as compared to similar patients who did not receive dobutamine hydrochloride. In animals, administration of dobutamine hydrochloride shortly after the ligation of coronary arteries reduces infarct size, when compared to controls receiving saline solution or dopamine. In other animals with experimental infarction who were given dobutamine hydrochloride at doses that increased both heart rate and myocardial contractility, there were electrocardiographic signs of increased ischaemia. Recent studies in animals suggest that functional deterioration and possible enlargement of experimental myocardial lesions during the administration of inotropic medicines including dobutamine hydrochloride is related to their chronotropic effect rather than to the positive inotropism. When dobutamine hydrochloride was infused at doses that produced significant inotropic effect with a minimal increase in heart rate, there was no evidence of enhanced myocardial damage.

Infusions of dobutamine hydrochloride for less than one hour in patients with congestive heart failure increase cardiac output and decrease pulmonary wedge pressure; however, haemodynamic improvements are not accompanied by increases in exercise tolerance. By contrast, longer infusions (up to 72 hours) or infusions that are repeated at regular intervals over several weeks or months do increase exercise tolerance and improve clinical status. This is true even though resting ventricular function is not always augmented.

The mechanism of the sustained improvement in ventricular function following prolonged or intermittent infusions of dobutamine hydrochloride is not understood. However, in studies involving prolonged infusions of dobutamine hydrochloride in humans, mitochondrial ultrastructural and biochemical changes have been reported, suggesting a basis for the protracted amelioration.

Dobutamine hydrochloride has been used in combination with dopamine. In general, the combination does not increase cardiac output more than does an equivalent dose of dobutamine hydrochloride alone. However, the combination of dobutamine hydrochloride and dopamine (a) increases systemic arterial pressure (which would be beneficial to hypotensive patients), (b) increases renal blood flow, urine flow, and sodium excretion, and (c) prevents the increase in ventricular filling pressure that tends to occur with dopamine alone, thus decreasing the risk of pulmonary congestion and oedema, especially in patients with compromised left ventricular function.

Dobutamine hydrochloride has also been used in combination with other vasodilators such as nitroglycerin or nitroprusside, especially in patients with ischaemic heart disease. This combination potentiates the increment in cardiac output and the decrement in systemic vascular resistance and ventricular filling pressure observed with either medicine alone. The heart rate-blood pressure product is either minimally increased or not changed by the concomitant administration of dobutamine hydrochloride and a vasodilator.

Dobutamine hydrochloride is a β-adrenergic agonist. Accordingly, its effects may be counteracted by β-adrenergic receptor antagonists. During treatment with β-antagonists, low doses of dobutamine hydrochloride will manifest varying degrees of a -adrenergic activity, such as vasoconstriction. Because the interaction between both dobutamine hydrochloride and the antagonists on the β receptors is reversible, these 2 drug classes will compete among themselves. Thus, higher doses of dobutamine hydrochloride will progressively counteract the effect of β-adrenergic receptor antagonists.

Paediatric Population

Dobutamine hydrochloride 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 heart rate and arterial blood pressure to increase more in children than in adults. Pulmonary wedge pressure may increase during infusion of dobutamine hydrochloride 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.

Dobutamine stress echocardiography

Ischaemic diagnostic: Due to the positive inotropic testing and in particular due to the positive chronotropic effects under dobutamine stress, the myocardial oxygen (and substrate) demand increases. With a pre-existing coronary artery stenosis, an insufficient increase of coronary blood flow leads to local hypoperfusion, which can be demonstrated on the echocardiogram in the form of a newly developed myocardial wall motility disorder in the respective segment.

Viability diagnostic: Viable myocardium, which is hypokinetic or akinetic (due to stunning, hibernation) on the echocardiogram, has a contractile functional reserve. This contractile functional reserve is particularly stimulated by the positive inotropic effects during dobutamine stress testing at lower doses (5-20 µg/kg/min). An improvement of the systolic contractility, i.e. increase of wall motility in the respective segment, can be shown on the echocardiogram.

5.2 Pharmacokinetic properties

Although the onset of action of dobutamine hydrochloride is within 1 to 2 minutes, as much as 10 minutes may be required to reach steady state plasma concentrations and peak effects with any given infusion rate. Steady state plasma concentrations are linearly related to infusion rates. At an infusion rate of 5 mcg/kg/min, the mean plasma concentration is approximately 100 ng/mL in patients with congestive heart failure.

Plasma clearance of dobutamine hydrochloride in humans is 2.4 L/min/m2, the volume of distribution is about 20% of body weight, and plasma elimination half-time is less than 3 minutes. The principal routes of disposition include methylation followed by conjugation. Metabolites are eliminated by

renal and biliary mechanisms. In human urine, the major excretion products include conjugates of dobutamine and 3-*o*-methyl dobutamine. The 3-*o*-methyl derivative is inactive.

Partial tolerance to dobutamine hydrochloride develops during prolonged continuous infusions and becomes statistically significant at 72 hours. The cardiac output response to a constant infusion of dobutamine hydrochloride at 72 hours is over 70% of that obtained at the end of 2 hours in patients with congestive heart failure. This phenomenon may be caused by a decrease (down-regulation) in the number of β-adrenergic receptors.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine hydrochloride in animals; dobutamine hydrochloride acts directly, and its effects are not dependent on presynaptic mechanisms.

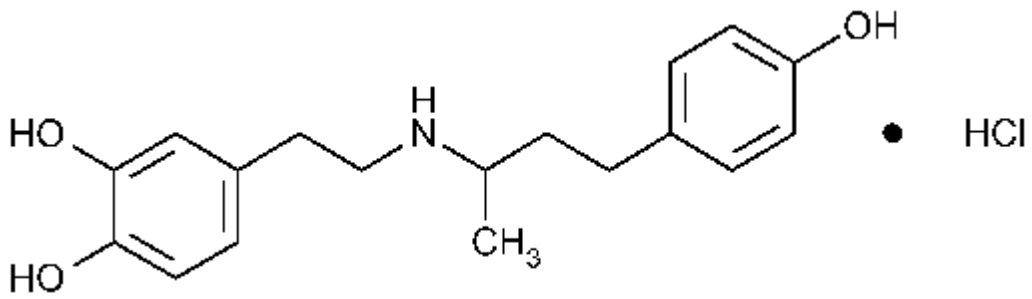
Paediatric population

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.

Other

The chemical name of dobutamine hydrochloride is (RS)-4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]ethyl]benzene-1,2-diol hydrochloride.



and enantiomer

The CAS number is 49745-95-1.
The empirical formula is C18H23NO3,HCl and the molecular weight is 337.9

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There are no studies concerning the mutagenic and carcinogenic potential of dobutamine. In view of the vital indications and the short duration of treatment these studies appear of minor relevance. Studies in rats and rabbits revealed no evidence of a teratogenic effect. An impairment of implantation and pre- and postnatal growth retardations were observed in rats at doses toxic to mothers. No influence on fertility was seen in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment)
Sodium metabisulfite
Water for injection

6.2 Incompatibilities

Do not add dobutamine to sodium bicarbonate injection 5% or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended dobutamine should not be mixed with other medicines in the same solution.

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

Dobutamine is incompatible with:

- alkaline solutions (e. g. sodium hydrogen carbonate)
- solutions containing both sodium metabisulfite and ethanol
- aciclovir
- alteplase
- aminophylline
- bretylium
- calcium chloride
- calcium gluconate
- cefamandol formiate
- cephalotine sodium
- cephazolin sodium
- diazepam
- digoxin
- etacrynic acid (sodium salt)
- furosemide
- heparin sodium
- hydrogen cortisone sodium succinate
- insulin
- potassium chloride
- magnesium sulfate
- penicillin
- phenytoin
- streptokinase
- verapamil.

Furthermore, known incompatibilities for sodium metabisulfite are:

- chloramphenicol
- cisplatin.

This medicinal product should not be mixed with other medicinal products except with those for which compatibility is proven.

6.3 Shelf life

In an un-opened container:
3 years.

Once opened or following dilution:
24 hours at 25°C.

Reconstitution and stability
Dobutamine must be diluted at the time of administration to at least 50 mL in an intravenous container with one of the following solutions. Glucose 5% injection, glucose 5% and sodium chloride 0.45% injection, glucose 5% and sodium chloride 0.9% injection, glucose 10% injection, lactated Ringer's injection or sodium chloride 0.9% injection.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Parenteral products which are hazy, discoloured or contain visible particulate matter should be discarded. Solutions containing dobutamine may exhibit a pink colour that, if present, will increase with time. This colour change is due to slight oxidation of the medicine, but there is no significant loss of potency during the reconstituted time periods stated above.

This medicine contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Do not refrigerate or freeze.
For storage conditions after dilution and first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Pack sizes of 1 and 5 ampoules, made of colourless, neutral glass, type I Ph.Eur, containing 20 ml concentrate for solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246
Telephone: (09) 815 2664.

9 DATE OF FIRST APPROVAL

15 August 2013

10 DATE OF REVISION OF THE TEXT

15 July 2021

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
15 July 2021	2 4.4, 4.5, 4.7, 4.8 8	• Reworded for better understanding. • Updated to align with current source document. • Update address details