# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dobutamine-hameln 250 mg/50 ml ampoule, solution for infusion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml of solution contains 5mg Dobutamine equivalent to 5.6mg Dobutamine HCl. Each 50ml ampoule contains 250mg Dobutamine equivalent to 280mg Dobutamine Hydrochloride.

For excipients, see 6.1

## 3 PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless or almost colourless solution

## 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 or cardiomyopathies. Dobutamine is also indicated for adults with cardiogenic or septic shock who are not severely hypotensive. Dobutamine can increase or maintain cardiac output during positive end expiratory pressure (PEEP) ventilation.
Dobutamine may also be used for cardiac stress testing in cases where exercise stress testing is not feasible or inadequate.

### 4.2 Posology and method of adminstration

Due to its short half-life dobutamine has to be administered by continuous intravenous infusion.
Dobutamine Hameln 250 mg/50 ml may be diluted if wanted. Diluents may be 5 % glucose solution, 0.9 % sodium chloride solution, Ringer-lactate or 0.45 % sodium chloride in 5 % glucose solution.

Note: Dobutamine Hameln 250 mg/50 ml may not be mixed with 5 % sodium bicarbonate solution or any other strong alkaline solution. Due to the risk of incompatibility Dobutamine Hameln 250 mg/50 ml is not recommended to be mixed in the same infusion as other medical substances.

Dobutamine Hameln 250 mg/50 ml should not be used in solutions for intravenous infusion containing both sodium metabisulphite and ethanol. Sulphite is a very reactive substance. Other drugs may not be added to the solution. In case of concomitant administration of other drugs different venous catheters should be used (c.f. 6.2. Incompatibilities).
The solution for infusion should be prepared under aseptic conditions immediately before use. The prepared solution should be used within 24 h or discarded. The diluted solution has to be protected from light and stored in the refrigerator. In principle, only clear and colourless solutions should be used. A slight pink discolouration, which may deepen with time, results from a slight oxidation of the drug, but there is no relevant loss of potency during the recommended storage time in case of adherence to the recommended precautions for storage.

Therapeutic dosage:
Dobutamine hydrochloride has to be dosed individually. 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, by measurement of cardiac output, central venous pressure and pulmonary capillary wedge pressure. There is evidence that partial tolerance develops with continuous infusions for 72 hours or more, therefore higher doses may be necessary to maintain the same effects.
It is recommended that treatment with dobutamine should be discontinued gradually.

Dosage in adults:
Most patients will respond satisfactorily to doses ranging from 2.5 to 10 µg/kg/min. Occasionally, however, a dose as low as 0.5 µg/kg/min will elicit a response. Rarely, a dose as high as 40 µg/kg/min is required.

Dosage in children**:**
The safety and efficacy of dobutamine for use in children have not been established.

The necessary infusion rate depends on the response of the patient and the occurrence of possible adverse events. The rate of infusion is increased at 10-30 minutes intervals until the desired haemodynamic effects are achieved or undesired effects prevent a further increase in dose.

The duration of the treatment depends on the clinical needs. Caution has to be exercised in case the dose exceeds 10 µg/kg/min or the treatment duration is longer than 72 hours.
An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops per minute. High concentrations should only be given with an infusion pump to ensure accurate dosing.

The following table may serve as a guide for the rate of infusion per kg body weight and minute.

| | Delivery rate (ml/min/kg) at concentrations of infusion solution of | | | |
|---|---|---|---|---|
| | 250 µg/ml* | 500 µg/ml** | 1000 µg/ml*** | 5000 µg/ml**** |
| infusion rate (µg/kg/min) | | | | |
| 0.5 | 0.002 | 0.001 | 0.0005 | 0.0001 |
| 1.0 | 0.004 | 0.002 | 0.0010 | 0.0002 |
| 2.5 | 0.010 | 0.005 | 0.0025 | 0.0005 |
| 5.0 | 0.020 | 0.010 | 0.0050 | 0.0010 |
| 7.5 | 0.030 | 0.015 | 0.0075 | 0.0015 |
| 10.0 | 0.040 | 0.020 | 0.0100 | 0.0020 |
| 12.5 | 0.050 | 0.025 | 0.0125 | 0.0025 |
| 15.0 | 0.060 | 0.030 | 0.0150 | 0.0030 |

* 250 mg dobutamine in 1 litre solution
** 500 mg dobutamine in 1 litre solution or 250 mg dobutamine in 500 ml solution
*** 1000 mg dobutamine in 1 litre solution, or 250 mg dobutamine in 250 ml solution
**** 250 mg dobutamine in 50 ml solution.

The final volume administered should be determined by the fluid requirements of the patient. Concentrations as high as 5,000 µg/ml (5 mg/ml) have been used in patients on a restricted fluid intake.

Dosage for cardiac stress testing:
The recommended dosage is an incremental increase in infusion rates from 5 µg/kg/min to 10, 20, 30 and a maximum of 40 µg/kg/min, each dose being infused for 3 minutes. In addition atropine may be added during further infusion of the peak dose in case of not achieving an endpoint with dobutamine alone. Continuous ECG monitoring is essential and the infusion terminated in the event of ST-segment depression of >0.2 mV (2 mm) measured 80 ms after the J point, a ST-segment elevation of >0.1 mV (1 mm) in patients without history of myocardial infarction, or any significant cardiac arrhythmias.

The infusion should also be terminated if the heart rate reaches 85% of the age-predicted maximum, systolic blood pressure rises above 220 mmHg or a symptomatic decrease in systolic blood pressure ≥ 40 mmHg from baseline,

new cardiac wall motion abnormalities, severe chest pain or any non-tolerable adverse effect occurs.

The dobutamine stress test should only be undertaken in units, where personnel specially trained in resuscitation and resuscitation equipment including a defibrillator are immediately available.

## 4.3 Contraindications

Hypersensitivity to dobutamine or sodium metabisulphite. Mechanical obstruction of ventricular filling or outflow. Hypovolaemia. Non-controllable serious ventricular arrhythmias.
In addition for cardiac stress test: unstable angina, uncontrolled hypertension, uncontrolled arrhythmias (including uncontrolled atrial fibrillation), known severe ventricular arrhythmias, electrolyte imbalance and severe anaemia.

## 4.4 Special warnings and special precautions for use

Dobutamine should only be used in specialist units in which adequate facilities are available for patient surveillance and the monitoring of responses. During dobutamine infusions heart rate, cardiac rhythm (by ECG), blood pressure, urine flow and infusion rate should be monitored continuously and, if possible cardiac output, central venous pressure and pulmonary capillary wedge pressure be controlled.

The dobutamine stress test should only be undertaken in units, where personnel specially trained in resuscitation and resuscitation equipment including a defibrillator are immediately available.

Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Patients with pre-existing hypertension appear to be at greater risk of developing a hypertensive response. 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 it has caused ventricular tachycardia or fibrillation. Because dobutamine facilitates atrioventricular conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses and therefore should be digitalised prior to administration of dobutamine.

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.

Particular care should be exercised when dobutamine is used in patients with acute myocardial infarction because 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.

As with other catecholamines dobutamine can also trigger an onset of angina in patients with ischaemic heart disease and consequently particular care should be exercised, when dobutamine is given to patients with ischaemic heart disease.
Particular caution has to be exercised when using dobutamine in patients treated with mono-aminoxidase (MAO) inhibitors and in patients with phaeochromocytoma or with hyper-thyroidism due to the increased catecholamine levels or sensitivity, which could result in marked increases in blood pressure, heart rate and higher incidence in arrhythmias.

Some haemodynamic effects of dobutamine may be quantitatively or qualitatively different in children compared to adults. Heart rate and blood pressure increases appear to be more frequent and more intense in children. Unlike in adults, pulmonary capillary wedge pressure may not be reduced in children, and it may even increase, especially in children under one year of age. Consequently, the use of dobutamine in children should be closely monitored.

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 baseline values, but rarely intervention may be required and reversibility may not be immediate.
Dobutamine should be used with caution in the presence of severe hypotension complicating cardiogenic shock

(mean arterial pressure less than 70 mmHg).
Before administration of dobutamine hypovolaemia should be corrected.

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 as dopamine or noradrenaline.
Like other drugs with $\beta_2$-agonist activity, dobutamine may produce slight reductions in serum potassium concentrations and rarely hypokalaemia may occur. Consideration should be given to monitoring serum potassium during dobutamine therapy.
Dobutamine may alter insulin and glucose plasma levels. Consequently in diabetic patients the glucose concentration should be controlled and the insulin dose adjusted if necessary.

During a prolonged continuous infusion (48-72 h) a decrease in haemodynamic response may occur, which makes an increase in dose necessary.
Dobutamine Hameln 5 mg/ml Amp. 50 ml contains sodium metabisulphite. This may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in certain susceptible individuals. The overall prevalence of sulphite sensitivity in the general population is unknown but probably low. Such sensitivity seems to occur more frequently in asthmatic than in non-asthmatic patients.

## 4.5 Interaction with other medicinal products and other forms of interaction

Pretreatment or concomitant administration of β-receptor blocking drugs may result in decrease in inotropic and chronotropic effects due to competitive binding to the β-receptor and in predominance of the $\alpha_1$-mediated effects resulting in peripheral vasoconstriction and increase in blood pressure.
Concomitant administration of α-blockers may result in predominance of the β-agonistic effects with increase in heart rate and peripheral vasodilation.
Peripheral vasodilators (e.g. nitrates, sodium nitroprusside) in combination with dobutamine may increase cardiac output and decrease systemic peripheral resistance and ventricular filling pressure more than either drug alone.

Concomitant use of dobutamine and MAO-inhibitors may result in marked increases in blood pressure and heart rate and in increased incidence of arrhythmias. Even life-threatening adverse effects may result as hypertensive crisis, cardiovascular collapse, intracranial haemorrhage and arrhythmias.
Concomitant administration of guanethidine and rauwolfia alkaloids with dobutamine might result in augmented increases in blood pressure and arrhythmia frequency. Theophylline was supposed to increase the heart rate response in one study.

Concomitant administration of dobutamine and ACE-inhibitors (e.g. captopril) may result in an increase in cardiac output accompanied by increased myocardial oxygen consumption, occurrence of chest pain and arrhythmias have been reported with this combination.
Concurrent use of dobutamine and dopamine increases systemic arterial pressure more markedly and prevents the increase in ventricular filling pressure seen with dopamine alone.
Concomitant use of dobutamine and peripheral vasoconstrictor agents as noradrenaline increases systemic arterial blood pressure more markedly.
According to animal studies volatile anaesthetics, especially cyclopropane and halothane, may interact with dobutamine, giving rise to ventricular arrhythmias.
Addition of atropine sulphate enhances the increases in heart rate induced by dobutamine and may counteract the deceleration in heart rate occasionally observed in dobutamine stress testing.

Pretreatment with a calcium chloride load was found to decrease the inotropic effects of dobutamine in one study.
Dobutamine may increase the clearance of lidocaine in patients with severe heart failure according to one study.
Dobutamine may interfere with the detection of chloramphenicol by HPLC.

## 4.6 Pregnancy and lactation

As there are no adequate data on the safety of dobutamine in human pregnancy, and it is not known whether dobutamine crosses the placenta, dobutamine should not be used during pregnancy unless potential benefits

outweigh the potential risks to the foetus and there are no safer therapeutic alternatives.
It is not known, whether dobutamine is excreted in milk, so caution should be exercised. If dobutamine treatment of the mother is required during lactation, breast feeding should be discontinued for the duration of treatment.

## 4.7 Effects on ability to drive and use machines

Due to the short duration of action of dobutamine no effects on the ability to drive or use of machines is to be expected shortly after the end of the infusion.

## 4.8 Undesirable effects

Therapeutic use:
An increase in heart rate by 5 to 15 beats per minute and in systolic blood pressure by 10-20 mmHg have been noted frequently. More pronounced increases in heart rate and blood pressure (especially in patients with preexisting hypertension) have been reported occasionally.
Precipitous decreases in blood pressure have occasionally been reported. Decreasing the infusion rate or (temporary) discontinuing of the infusion of dobutamine in general results in rapid return of blood pressure to baseline values. In rare cases, however, symptomatic treatment may be required and reversibility may not be immediate.
Occasionally a slight vasoconstriction has been observed especially in patients pretreated with β-blockers.
Occasionally supraventricular or ventricular arrhythmias, primarily ventricular premature beats, may occur especially in patients with preexisting arrhythmias. In rare cases dobutamine treatment was associated with atrial fibrillation and serious ventricular arrhythmias as ventricular tachycardia or fibrillation. Rapid ventricular response has been observed in patients with atrial fibrillation or atrial flutter.

The following adverse effects have been reported in 1-3% of patients: nausea, vomiting, headache, anginal pain, non-specific chest pain, palpitations, shortness of breath, tingling sensation or paraesthesia. In rare cases tremor or flushing have been observed.
Dobutamine may induce a mild reduction in serum potassium concentrations but rarely hypokalaemia has been observed.
Administration of dobutamine can induce a mild reduction in serum potassium concentration, but rarely hypokalaemia has been induced.

At high doses urinary urgency was reported by some patients.
Reactions suggestive of hypersensitivity including skin rash, fever, eosinophilia and bronchospasm have been reported occasionally.
Pruritus of the scalp during infusion of dobutamine has been observed. In isolated cases thrombocytopenia and petechial bleeding have been reported.
Local reactions at the site of the intravenous infusion as phlebitis have occasionally been reported. Following extravasation local inflammations have been described and in isolated cases dermal necroses (especially at high concentrations of the infusion solution).

Dobutamine Hameln 5 mg/ml Amp. 50 ml contains sodium metabisulphite, which may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes.

During stress test:
The adverse effects seen during dobutamine stress test are in principle those seen with therapeutic use. However, the incidence of dose-related adverse effects is increased. Chest pain, ST-segment deviations, dyspnoea, palpitations, hypotension, cardiac arrhythmias (primarily atrial and ventricular premature beats) are common. Serious ventricular arrhythmias, however, are rare.
Development of dynamic cardiac outflow obstruction and of heart rate deceleration (after initial increase) are common. Hypertension has been reported occasionally.
In rare cases coronary spasms (without myocardial necrosis) have been induced and myocardial infarctions, in part occurring after cessation of the infusion.
Other adverse effects as chills, tremor, nausea, vomiting, flushing, headache, nervousness and anxiety occur occasionally.

## 4.9 Overdose

The symptoms of overdose may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, fatigue, shortness of breath and chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachyarrhythmias, myocardial ischaemia and ventricular fibrillation. Hypotension may result from vasodilation.
Due to the short duration of action of dobutamine, usually only a reduction in infusion rate or a transient cessation of infusion are necessary until stabilisation of the patient. Symptomatic treatment should be provided is necessary, blood gases and electrolytes corrected.

Serious ventricular arrhythmias may be treated with lidocaine or a β-blocker (e.g. propranolol). Forced diuresis, peritoneal dialysis or charcoal haemoperfusion have not been established as beneficial.
If dobutamine hydrochloride is ingested unpredictable absorption may occur. The use of activated charcoal is recommended.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Dobutamine facilitates atrioventricular conduction and shortens the AV-node recovery time. Dobutamine may enhance or induce ectopic activity.
Dobutamine increases - as all inotropic agents - blood flow to poorly ventilated pulmonary areas. The resulting decrease in arterial oxygen saturation, however is compensated in general by the increase in oxygen delivery.
Dobutamine does not act on dopaminergic receptors and hence does not selectively dilate renal or splanchnic vessels. However, dobutamine may improve renal blood flow, glomerular filtration rate, urinary output and urinary sodium excretion by increasing cardiac output and inducing vasodilatation.

## 5.2 Pharmacokinetic properties

Following i.v. administration the onset of action of dobutamine occurs within 2 minutes, peak effects and steady state plasma concentrations within 10 minutes after initiation of a particular infusion rate. Steady state plasma concentrations are related linearly to the infusion rate. The effects of the drug ceases shortly after discontinuation of the infusion.

It is not known if dobutamine crosses the placenta or is distributed into milk.
The plasma half-life is about 2 minutes. The principal metabolic pathways are methylation by catecholamine-O-methylase (COMT) and conjugation. Metabolites are excreted primarily in urine and to a minor extent in bile. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl-dobutamine.

## 5.3 Preclinical safety data

Acute toxicity:
In the mouse and rat the intravenous $LD_{50}$ of dobutamine was 100 mg/kg, in the dog 40 mg/kg. At toxic doses immediate collapse of short duration was observed. Surviving animals showed hyperactivity with increased heart and respiratory rates, mydriasis and salivation.

Repeated dose toxicity:
Over 14 days rats tolerated daily intravenous doses of 10 mg/kg dobutamine, dogs those of 4x15 mg/kg/d or 50 µg/kg/min continuously. Cardiotoxic effects in dogs were associated with early ECG-signs.
In studies over 30 days dobutamine at doses up to 24 mg/kg/d in dogs and up to 80 mg/kg/d in rats was associated with dose-dependent hypertrophy of the acinus cells of the parotid gland and with myocardial damage at the high and to a minor extent medium doses. In rats the highest dose was associated with a 100% lethality within 19 days. At 2 mg/kg/d in rats and 1.4 mg/kg/d in dogs no toxic effects were seen.

When dobutamine was given to dogs at doses up to 6 mg/kg/d over 6 months only clinical symptoms (tachycardia

with increased amplitudes, flushing, vomiting, tremor, prostration and salivation) were observed but no other drug-induced damage.

Mutagenic and carcinogenic activity:
No studies are available.

Reproduction toxicity:
Studies in rats and rabbits revealed no indications for a teratogenic effect. In impairment of implantation and pre- and postnatal growth retardations were observed rats at dobutamine doses toxic to the mothers. No influence on fertility was seen in studies in rats.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium metabisulphite, sodium chloride, hydrochloric acid and water for injection.

## 6.2 Incompatibilities

Due to the risk of incompatibility Dobutamine Hameln 250 mg/50 ml is not recommended to be mixed in the same infusion as other medical substances.

Dobutamine Hameln 250 mg/50 ml should not be mixed or administered simultaneously with:
**alkaline solutions** (e.g. sodium bicarbonate) and solutions containing both sodium metabisulphite and ethanol, acyclovir, aminophylline, bretylium tosylate, bumetanide, calcium chloride, calcium gluconate, cefamandole nafate, cephalotine sodium, cephazoline sodium, diazepam, digoxin, ethacrynate sodium, furosemide, heparin sodium, hydrocortisone sodium succinate, insulin, magnesium sulfate, penicillin, phenytoin, potassium chloride, streptokinase, verapamil.

Sodium metabisulphite is a very reactive substance. Therefore a degradation of thiamine (vitamin $B_1$) may be possible.

## 6.3 Shelf Life

Shelf-life before first opening:
3 years.

Shelf-life after first opening and/or dilution:
From the microbiological point of view, the solutions or dilutions 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 to 8 °C.

## 6.4 Special precautions for storage

Store below 25°C. Keep in the outer container.

## 6.5 Nature and contents of container

1 and 5 ampoules made of colourless, neutral type 1 Ph. Eur. glass containing 50 ml solution.

## 6.6 Instructions for use and handling

In case of concomitant administration of other drugs different venous catheters should be used (c.f. 6.2. Incompatibilities).
Dobutamine Hameln 250 mg/50 ml may be diluted if wanted. Diluents may be 5% glucose solution, 0.9% sodium chloride solution, Ringer-lactate, or a solution of 0.45% sodium chloride and 5% glucose solution.

The solution for infusion should be prepared under aseptic conditions immediately before use. In principle, only clear and colourless solutions should be used. A slight pink discolouration, which may deepen with time, results from a slight oxidation of the drug, but there is no relevant loss of potency during the recommended storage time in case of adherence to the recommended precautions for storage.

Any unused portion has to be discarded.

## 7 MARKETING AUTHORISATION HOLDER

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## 8 MARKETING AUTHORISATION NUMBER

PA 971/2/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th November 2003

## 10 DATE OF REVISION OF THE TEXT

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