# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dobutamine Pfizer 12.5 mg/ml Concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 12.5 mg of dobutamine (as 14.01 mg dobutamine hydrochloride).
Each 20 ml ampoule contains 250 mg of dobutamine (as 280.2 mg dobutamine hydrochloride).
Each 1 ml contains 0.15 mg of Sodium metabisulphite.
Each 20 ml contains 3.0 mg of Sodium metabisulphite.
For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
Clear, colourless or slightly yellow solution

pH between 2.50 and 4.00

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Dobutamine is indicated for adults who require positive inotropic support in the treatment of low output cardiac failure normally associated with myocardial infarction, open-heart surgery, cardiomyopathies, septic shock and cardiogenic shock.

Dobutamine can also be used for cardiac stress testing, in cases when exercise stress testing is not feasible.

### 4.2 Posology and method of administration

Method of administration

Dobutamine Concentrate should be diluted before use and administered by IV infusion only.

The concentration of the dobutamine administered depends upon the dosage and fluid requirements of the individual patient. The final concentrations generally used for perfusion are 250 micrograms/ml, 500 micrograms/ml or 1000 micrograms/ml. For special precautions for storage of the prepared diluted infusion see section 6.4. High concentrations of dobutamine should only be given with an infusion pump or other suitable apparatus to ensure accurate dosage. Due to its short half-life dobutamine should be administered as a continuous intravenous infusion.

Dobutamine should be administered intravenously through an intravenous needle or catheter. The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate solution.

For instructions on dilution of the medicinal product before administration, see section 6.6.

**Dosage for Infusion delivery systems:**
One ampoule Dobutamine 12.5 mg/ml (250 mg/20 ml) diluted to a solution volume of 500 ml (final concentration 0.5 mg/ml) with any of the approved diluents (see section 6.6).

| Dosage range | | Specifications in ml/h* (drops/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(drops/min) | 15<br>(5) | 21<br>(7) | 27<br>(9) |
| Medium<br>5 µg/kg/min | ml/h<br>(drops/min) | 30<br>(10) | 42<br>(14) | 54<br>(18) |
| High<br>10 µg/kg/min | ml/h<br>(drops/min) | 60<br>(20) | 84<br>(28) | 108<br>(36) |

* For double concentration, i.e. 500 mg Dobutamine added to 500 ml, or 250 mg added to 250 ml solution, infusion rates must be halved.

The dose to be administered can be calculated taking into account the table below. Infusion rates in millilitres/min can be obtained by multiplying infusion rates for each concentration (ml/kg/min) by patient's weight (kg).

| | One (1) ampoule | Two (2) ampoules | Four (4) ampoules |
|---|---|---|---|
| | 250 mg dobutamine in 1000 ml of solution for infusion | 500 mg dobutamine in 1000 ml of solution for infusion | 1000 mg dobutamine in 1000 ml of solution for infusion |
| | 250 micrograms/ml | 500 micrograms/ml | 1000 micrograms/ml |
| Dose micrograms/kg/min | Infusion rate ml/kg/min | Infusion rate ml/kg/min | Infusion rate ml/kg/min |
| 2.5 | 0.01 | 0.005 | 0.0025 |
| 5 | 0.02 | 0.01 | 0.005 |
| 7.5 | 0.03 | 0.015 | 0.0075 |
| 10 | 0.04 | 0.02 | 0.01 |
| 12.5 | 0.05 | 0.025 | 0.0125 |
| 15 | 0.06 | 0.03 | 0.015 |

*Dosage for syringe pumps:*
One ampoule Dobutamine 12.5 mg/ml (250 mg/20 ml) diluted to a solution volume of 50 ml (final concentration 5 mg/ml) with any of the approved diluents (see section 6.6).

| Dosage range | | Specifications in ml/h (ml/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(ml/min) | 1.5<br>(0.025) | 2.1<br>(0.035) | 2.7<br>(0.045) |
| Medium<br>5 µg/kg/min | ml/h<br>(ml/min) | 3.0<br>(0.05) | 4.2<br>(0.07) | 5.4<br>(0.09) |
| High<br>10 µg/kg/min | ml/h<br>(ml/min) | 6.0<br>(0.10) | 8.4<br>(0.14) | 10.8<br>(0.18) |

Posology

*Adults:*

Inotropic support of the myocardium:
The usual dose is 2.5 to 10 micrograms/kg/min, which should be adjusted according to the patient's heart rate, blood pressure, cardiac output and urine output. The infusion must be started at a rate of 2.5 micrograms/kg/min and the dose may be increased in intervals of 10-30 minutes until desired hemodynamic response is achieved or until side effects, such as excessive tachycardia, arrhythmia, headache or tremor limit a further increase in dosage. The dose should be adjusted individually according to heart rate and rhythm, blood pressure and urinary flow. Occasionally, a dose as low as 0.5 micrograms /kg/min will elicit a response. Up to 40 micrograms/kg/min may occasionally be required, but this is rare.

During prolonged continuous infusion (48-72 hours), a decrease in haemodynamic response may occur, which makes an increase in dose necessary.

Dosage for cardiac stress testing:
The use of dobutamine in cardiac stress testing 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 including the availability of a defibrillator and personnel specially trained in resuscitation are present.

The recommended dosage is an incremental increase in infusion rates from 5 micrograms/kg/minute to 10, 20, 30 and a maximum of 40 micrograms/kg/minute, each dose being infused for 3 minutes. In addition atropine can be added during further infusion of the peak dose. Continuous electrocardiogram (ECG) monitoring is required and the infusion may be terminated in the event of ST-segment depression of > 0.2 mV (2 mm) measured 80 ms after the J point, a ST-segment elevate of > 0.1 mV (1 mm) in patients without history of myocardial infarction, or any significant cardiac arrhythmias.

The infusion of dobutamine should 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.

*Elderly:*

No variation in dosage is suggested. Close monitoring is required for blood pressure, urine flow and peripheral tissue perfusion.

Cardiac stress testing: When used as an alternative to exercise for cardiac stress testing the recommended dose should start at 5 micrograms/kg/minute, and the dose should be increased incrementally by 5 micrograms/kg/minute every 8 minutes, to a maximum rate of 20 micrograms/kg/minute. 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

*Paediatric Patients*

Doses of 1 to 15 µg dobutamine/kg/min have been administered. 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 µg dobutamine/kg/min. The required dose for children should be titrated in order to allow for the supposedly smaller “therapeutic width” in children. An initial dose of 0.5 micrograms/kg/min is recommended, which is increased every 10-30 minutes until reaching the desired response.

## 4.3 Contraindications

- Patients with known or suspected hypersensitivity to dobutamine, sodium metabisulphite or other sulphates or to any of the other excipients.
- Patients with marked mechanical obstruction affecting ventricular filling or outflow, or both, such as cardiac tamponade, severe valvular aortic stenosis, constrictive pericarditis, hypertrophic obstructive cardiomyopathia or idiopathic hypertrophic subaortic stenosis.
- Patients with hypovolaemia unless it has been corrected by volume replacement.
- Uncontrolled serious ventricular arrhythmias.
- In addition, for cardiac stress test: Recent myocardial infarction (within 30 days), aortic dissection, aortic aneurysm, unstable angina, uncontrolled hypertension, uncontrolled arrhythmias (including uncontrolled atrial fibrillation), known severe ventricular arrhythmias, electrolyte imbalance and severe anaemia.
- Phaeochromocytoma

## 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. Dobutamine increases atroventricular conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

There is a possibility that dobutamine can cause a significant increase in heart rate or excessive increase in arterial pressure which may intensify or extend myocardial ischaemia, cause anginal pain and ST segment elevation, therefore care should be exercised following myocardial infarction (see section 4.3).

Dobutamine will not improve haemodynamics in most patients with mechanical obstruction affecting ventricular filling or outflow, or both (see section 4.3).

Inotropic response may be inadequate in patients with markedly reduced ventricular compliance, e.g. with cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis (see section 4.3).

Via competitive receptor inhibition, the catecholaminergic effect of dobutamine can be reduced with simultaneous administration of a beta receptor blocker. In addition, the alpha effects predominant at that time may cause a peripheral vasoconstriction with a consequent increase of blood pressure.

*Administration*
Before administration of dobutamine, hypovolaemia should be corrected with an appropriate plasma volume expander (see section 4.3). Like other drugs with beta-2-agonist activity, dobutamine may produce slight reductions in serum potassium concentrations and hypokalaemia may occur occasionally. Consideration should be given to monitoring serum potassium during dobutamine therapy.

During administration of dobutamine, heart rate and rhythm, arterial blood pressure, and infusion rate should be monitored closely. When starting therapy, electrocardiographic monitoring is recommended until a stable response is obtained.

*Caution*
Dobutamine should be used with caution in severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70 mm Hg). If the blood pressure drops quickly, decreasing the dose or stopping the infusion typically results in a return to base-line blood pressure values.

Occasionally intervention may be required and reversibility may not be immediate.

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 use of a peripheral vasoconstrictor agent e.g. noradrenaline or dopamine.

Dobutamine Concentrate for solution for infusion contains sodium metabisulphite in the formulation. 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 is probably low; such sensitivity seems to occur more frequently in asthmatic patients (see section 4.3).

Dobutamine should only be used under the direct supervision of physicians to whom facilities for regular, intensive monitoring of cardiovascular and renal parameters, in particular, blood volume, myocardial contractility, electrocardiography, urine flow rate, and blood and pulse pressure and, if possible, cardiac output and pulmonary wedge pressure (PWP) are available.

After cessation of a longterm therapy (more than 7 days) with dobutamine a decrease in cardiac output and an increase in PWP was observed.

In patients with pre-existing hypertonia an increase in blood pressure could occur.

Since the effect of dobutamine on impaired renal and hepatic function is not known, close monitoring is advisable.

Intravenous continuous dobutamine is of limited benefit and may in fact be harmful to patients with advanced heart failure, with respect to quality of life and survival rates.

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.

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

As with other catecholamines, dobutamine may trigger an onset of angina in patients with ischaemic heart disease and consequently particular care should be exercised when dobutamine is administered to patients with ischaemic heart disease.

Particular caution has to be exercised when using dobutamine in patients treated with monoamine oxidase inhibitors (MAOs) and in patients with pheochromocytoma or with hyperthyroidism due to the increased catecholamine levels or sensitivity, which could result in marked increases in blood pressure, heart rate and higher incidence of arrhythmias

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.

Dobutamine stress echocardiography

Because of possible life-threatening complications the use within the scope of ischemia and vitally diagnostics is only allowed by a physician with sufficient personal experience in stress echocardiography.

Dobutamine stress echocardiography within the scope of ischemia and vitality diagnostics must be discontinued if one of the following diagnostic endpoints occurs:
- Reaching the age-predicted maximal heart rate [(220-age in years) x0.85],
- systolic blood pressure decrease >20 mmHg,
- blood pressure increase to >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 > 1 wall segment (16-segment model),
- increase of endsystolic volume,
- development of repolarisation abnormality (due to ischemia horizontal or down sloping ST segment depression >0.2 mV at an interval of 80 (60) ms after the J point compared to baseline, progressive or monophasic ST segment elevation >0.1 mV in patients without a previous myocardial infarction,
- reaching peak dose.

Also in case of serious complications (see section 4.8) a Dobutamine stress echocardiography has to be immediately disrupted.

After termination of infusion, patients must be monitored until stabilised.

This medicinal product contains 0.0504 mmol (1.160 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

Beta-adrenergic blocking agents

In animals the cardiac effects of dobutamine are antagonised by beta-adrenergic blocking agents such as propranolol and metoprolol, resulting in predominance of alpha-adrenergic blocking agents and increased peripheral resistance.

Conversely, alpha-adrenergic blockade may make the beta 1 and beta 2 effects apparent, resulting in tachycardia and vasodilatation.

The addition of dipyridamole to dobutamine for echocardiography can cause potentially hazardous hypotension. The combination should not be used in patients suspected of coronary heart disease.

Dobutamine stress echocardiography

In the case of anti-anginal therapy, in particular heart rate lowering agents like beta-blockers, the ischemic reaction to stress is less pronounced or may be nonexistent altogether.
Therefore antianginal therapy may need to be withheld for 12 hours prior to the Dobutamine stress echocadiography.

When adding atropine at the highest titration level of Dobutamine, the following can be observed:

Due to the prolonged duration of the stress echocardiography protocol, the higher total dose of Dobutamine and the simultaneous administration of atropine, there is an increased risk of adverse reactions.

General anaesthetics

Ventricular arrhythmias have been reported in animals receiving usual doses of dobutamine during halothane or cyclopropane anaesthesia; therefore, caution should be exercised when administering dobutamine to patients receiving these anaesthetics.

Concomitant use of dobutamine and MAOIs may result in marked increases in blood pressure and heart rate and in increased incidence of arrhythmias.

Even life-threatening events such as hypertensive crisis, cardiovascular collapse, intracranial haemorrhage and arrythmias may result.

Pre-treatment or concomitant administration of ß-receptor blocking drugs may result in decrease in inotropic and chronotropic effects due to competitive binding to the ß-receptor and in predominance of the alpha1-mediated effects resulting in peripheral vasodilatation.

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 theophylline with dobutamine resulted in an increase in the heart rate, in one clinical study.

Concurrent use of dobutamine and dopamine increases systemic arterial pressure markedly and prevents the increase in ventricular filling pressure seen with dopamine alone.

Concomitant use of dobutamine and peripheral vasoconstrictor agents such as noradrenaline increases systemic arterial blood pressure more markedly, than either drug alone.

Concomitant administration of dobutamine and ACE-inhibitors (e.g. captopril) may result in an increase in cardiac output accompanied by increased myocardial oxygen consumption. The occurrence of chest pain and arrhythmias has been reported with this combination.

The effects of dobutamine may be enhanced by the concomitant use with entacapone. The hypertensive effects of dobutamine may be antagonised by antipsychotics.

There is an increased risk of hypertension when dobutamine is given with doxapram.
There is an increased risk of ergotism when dobutamine is given with ergotamine and methysergide.

Concomitant use of dobutamine and oxytocin may cause hypertension (due to the enhanced vasopressor effects).

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 cardiac stress testing.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the safety of dobutamine in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition and post-natal development, but it is not known whether dobutamine crosses the placenta (see section 5.3). The potential risk for humans is unknown. Dobutamine should not be used during pregnancy unless the potential benefits to the woman outweigh the potential risks to the fetus.

Lactation
It is not known whether dobutamine is excreted in animal or human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with dobutamine should be made taking into account the benefit of breast-feeding to the child and the benefit of dobutamine therapy to the woman.

## 4.7 Effects on ability to drive and use machines

Not relevant in view of the indications for use and the short half-life of dobutamine.

## 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.

*The following terminologies have been used in order to classify the occurrence of undesirable effects:*

| | |
|---|---|
| Very common | *(≥ 1/10)* |
| Common | *(≥ 1/100 to < 1/10)* |
| Uncommon | *(≥ 1/1000 to < 1/100)* |
| Rare | *(≥ 1/10000 to < 1/1000)* |
| Very rare | *(< 1/10000)* |
| *Not known* | *(cannot be estimated from the available data)* |

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Immune system disorders:*
Common: Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported.
Rare: Sodium metabisulphite may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes (see section 4.4).

*Metabolism and nutrition disorders:*
Very rare: As with other catecholamines, decreases in serum potassium concentrations have occurred. Consideration should be given to monitoring serum potassium.

*Nervous system disorders:*
Common: Headache
Very rare: Myoclonus has been reported in patients with severe renal failure receiving dobutamine.

*Cardiac disorders:*
Very common: Increased heart rate, palpitations, severe chest pain, irregular heartbeats, arrhythmia, ventricular tachycardia, coronary artery spasm, electrocardiogram ST segment elevation.
Uncommon: Atrial fibrillation, ventricular fibrillation, left ventricular outflow tract obstruction.
Very rare: myocardial ischaemia, myocardial infarction, eosinophilic myocarditis, fatal cardiac rupture during dobutamine stress testing (see section 4.4).

*Vascular disorders:*
Common: Hypertension. Marked increase in systolic blood pressure indicates overdose (see also section 4.5).
Uncommon: Hypotension (see sections 4.4 & 4.5). Slight vasoconstriction, especially in patients with pre-treated with ß-blockers.

*Respiratory, thoracic and mediastinal disorders:*
Common: Shortness of breath, bronchospasm, asthma (see *Immune system disorders*).

*Gastrointestinal disorders:*
Common: Nausea.

*Renal and urinary disorder:*
Not known: urinary urgency

*General disorders and administration site conditions:*
Common: Non-specific chest pain.
Rare: Phlebitis has occasionally been reported and local inflammatory changes have been described following inadvertent infiltration.
Very rare: Cutaneous necrosis

## 4.9 Overdose

Overdose has been rarely reported.

Symptoms
The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, fatigue 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 vasodilation. The duration of action of dobutamine is generally short (half-life, approximately 2 minutes).

Treatment
Due to the short duration of action of dobutamine, usually only a reduction in infusion rate or a transient cessation of infusion is necessary until stabilisation of the patient.

Temporarily discontinue dobutamine until the patient's condition stabilises. The patient should be monitored and any appropriate resuscitative measures started immediately.

Forced diuresis, peritoneal dialyses, 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

Pharmacotherapeutic group: cardiac stimulants excluding cardiac glycosides, adrenergic and dopaminergic agents

ATC code: C01CA07

Dobutamine is a selective beta-adrenergic agonist whose mechanism of action is complex.

It is believed that the beta-adrenergic effects result from stimulation of adenyl cyclase activity. In therapeutic doses, dobutamine also has mild beta-2 and alpha-1 adrenergic receptor agonist effects, which are relatively balanced and result in minimal net direct effect on systemic vasculature. 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 beta-1-adrenergic stimulation, experimental evidence suggests that alpha-1-adrenergic stimulation may also be involved and that the alpha-1-adrenergic activity results mainly from the (-)-stereoisomer of the drug.

The beta-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. 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.

Dobutamine facilitates atrioventricular 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. Dobutamine does not seem to affect dopaminergic receptors and causes no renal or mesenteric vasodilation; 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

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Studies on the mutagenic or carcinogenic potential of dobutamine have not been conducted. Studies in rats and rabbits revealed no evidence of fetal harm or teratogenic effect. No influence on fertility was seen in rats.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium metabisulphite (E223)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for Injections

## 6.2 Incompatibilities

Dobutamine Concentrate has been reported to be incompatible with alkaline solutions and should not be mixed with sodium bicarbonate 5%, or other strong alkaline solutions i.e. aminophylline, furosemide. Precipitation has occurred with bumetanide, calcium gluconate, insulin, diazepam and phenytoin. Because of the potential physical incompatibilities, Dobutamine Concentrate should not be mixed with other drugs in the same solution.

Dobutamine should not be used with drugs or diluents containing bisulphites or ethanol.
This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

## 6.3 Shelf life

2 years

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.
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 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Prior to first use, do not store above 25°C.

Infusions must be aseptically prepared.

For storage conditions of the diluted medicinal product, see section 6.3.

Discard any unused product.

## 6.5 Nature and contents of container

20 ml clear glass ampoule (type I) with a pack size of 5 and 1 ampoules.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Dobutamine Concentrate should be diluted before use and administered by IV infusion only.

The final concentrations generally used for perfusion are 250 micrograms/ml, 500 micrograms/ml or 1000 micrograms/ml. See section 4.2 for method and duration of administration.

The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate solution.

Solutions of dobutamine hydrochloride may have a pink discolouration. This discolouration, which will increase with time, results from a slight oxidation of the drug. However, there is no significant loss of drug potency within the recommended maximum in-use storage time of 24 hours at 2°C - 8°C.

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

## 7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park
Citywest Business Campus
Dublin 24
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA 822/46/1

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

Date of first authorisation: 19th August 2011

## 10 DATE OF REVISION OF THE TEXT