

Dobutamine Injection USP 250mg/5ml, 250mg/20ml

1. Name of the medicinal product

**Dobutamine Injection USP 250mg/5ml
Taj Pharma**

Dobutamine Injection USP 250mg/20ml Taj Pharma

2. Qualitative and quantitative composition

a) Dobutamine Injection USP 250mg/5ml Taj Pharma

Each ml contains:

Dobutamine Hydrochloride equivalent to dobutamine	50mg
Sodium metabisulfite	0.24mg
Water for injection	q.s

b) Dobutamine Injection USP 250mg/20ml

Each ml contains:

Dobutamine Hydrochloride equivalent to dobutamine	12.5mg
Sodium metabisulfite	0.24mg
Water for injection	q.s

50 ml ampoule/vial

1 ml contains 5 mg dobutamine.

Excipient with known effect:

This medicine contains less than 1mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium-free'.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion

The product is a clear, colourless or almost colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Dobutamine is indicated for patients who require a positive inotropic support in the treatment of cardiac decompensation due to depressed contractility.

In cardiogenic shock characterised by heart failure with severe hypotension and in case of septic shock Dobutamine may be useful if added to dopamine in case of disturbed ventricular function, raised filling pressure of the ventricles and raised systemic resistance.

Dobutamine may also be used for detection of myocardial ischaemia and of viable myocardium within the scope of an echocardiographic examination (dobutamine stress echocardiography), if patients cannot undergo a period of exercise or if the exercise yields no information of value.

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."

4.2 Posology and method of administration

Dobutamine doses must be individually adjusted.

The required rate of infusion depends on the patient's response to therapy and the adverse reactions experienced.

Dosage in adults:

According to experience, the majority of patients respond to doses of 2.5-10 µg dobutamine/kg/min. In individual cases,

doses up to 40 µg dobutamine/kg/min have been administered.

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 hemodynamic 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.

Tables, showing infusion rates with different initial concentrations for various dosages:

Dosage for infusion delivery systems

One ampoule or vial Dobutamine 5 mg/ml (250 mg in 50 ml) diluted to a solution

volume of 500 ml (final concentration 0.5 mg/ml)

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

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

Dosage for syringe pumps

One ampoule or vial Dobutamine 5 mg/ml (250 mg in 50 ml) undiluted (final concentration 5 mg/ml)

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

The chosen syringe pump must be suitable for the volume and rate of administration.

For detailed information about suitable solutions for dilution please see section 6.6.

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 (see method and duration of application) is reached.

If no endpoint is reached atropine sulfate 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.

The experience in children and adolescents is limited to the treatment of patients requiring positive inotropic support.

Method and duration of administration

Dobutamine 5 mg/ml (250 mg in 50 ml) ampoule or vial

Only for intravenous infusion (syringe pump). Dilution is not required.

Intravenous infusion of dobutamine is also possible after dilution with compatible infusion solutions such as: 5% glucose solution, 0.9% sodium chloride or 0.45% sodium chloride in 5% glucose solution. (For detailed information for dilution please see section 6.6.) Infusion solutions should be prepared immediately before use. (For information on shelf life, see section 6.3.)

Due to its short half-life, dobutamine must be administered as a continuous intravenous infusion.

The dose of dobutamine should be gradually reduced when discontinuing therapy.

The duration of treatment depends on the clinical requirements and is to be determined by the physician and should be as short as possible.

If dobutamine is administered continuously for more than 72 hours, tolerance may occur, requiring an increase in the dose.

During the course of dobutamine administration, heart rate, heart rhythm, blood pressure, diuresis and infusion rate should be closely monitored. Cardiac output, central venous pressure (CVP) and pulmonary capillary pressure (PCP) should be monitored if possible.

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

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.

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

Dobutamine must not be used for the treatment of patients with bronchial asthma who are hypersensitive to sulfites.

A local increase or decrease of coronary blood flow, which may have an impact on the myocardial oxygen demand, has been observed with dobutamine therapy. The clinical characteristics of patients with severe coronary heart disease may deteriorate, in particular if dobutamine therapy is accompanied by a considerable increase in the heart rate and/or blood pressure. Therefore, as with all positive inotropes, the decision to use dobutamine to treat patients with cardiac ischaemia must be made for each case individually.

Due to the risk of arrhythmias and the uncertainty about long term effects on

myocardial dysfunction, inotropic agents, such as dobutamine, should be used with caution in the treatment of Acute Heart Failure (AHF).

As alterations in serum potassium level may occur, the potassium level should be monitored.

If dobutamine is administered continuously for more than 72 hours, tolerance phenomena (tachyphylaxis) may occur, requiring dosage increase.

Precipitous decreases in blood pressure (hypotension) 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 may interfere with HPLC determination of chloramphenicol.

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.

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.

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

- reaching the age-predicted maximal heart rate $[(220 - \text{age in years}) \times 0.85]$,
- 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.

Dobutamine contains **sodium metabisulfite** (E 223), which may rarely cause allergic reactions (hypersensitivity) and asthma-like symptoms (bronchospasm).

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

4.5 Interaction with other medicinal products and other forms of interaction

Via competitive receptor inhibition, the sympathomimetic effect of dobutamine can be reduced by simultaneous administration of a beta receptor blocker. In addition, the alpha agonistic effects may cause peripheral vasoconstriction with a consequent increase in blood pressure.

With simultaneous alpha-receptor blockade, the predominating beta-mimetic effects may cause tachycardia and peripheral vasodilatation.

Simultaneous administration of dobutamine and primarily venous acting vasodilators (e.g. nitrates, sodium nitroprusside) may cause a greater increase of cardiac output as well as a more pronounced decrease of peripheral resistance and ventricular filling pressure than administration of one of the individual substances alone.

Administering dobutamine to diabetic patients may cause increased insulin demand. In diabetic patients insulin levels should be checked when starting dobutamine therapy, changing the rate of infusion and discontinuing the infusion. If

necessary the insulin dose must be adjusted as required.

Simultaneous administration of high doses of dobutamine with ACE inhibitors (e.g. captopril) may cause an increase in cardiac output, accompanied by increased myocardial oxygen consumption. Chest pain and rhythm disturbances have been reported in this context.

Dobutamine combined with dopamine causes – depending on the dopamine dosage and in contrast to its sole administration – a more distinct increase of blood pressure as well as a decrease or no change of ventricular filling pressure.

Sodium metabisulfite is a very reactive compound. It must therefore be assumed that thiamine (vitamin B₁) co-administered with the preparation is catabolised.

Caution should be exercised when administering dobutamine with inhaled anaesthetics, since concomitant use may increase the excitability of the myocardium and the risk of ventricular extrasystoles.

Dobutamine stress echocardiography

In the case of anti-anginal therapy, in particular heart rate lowering agents like beta-blockers, the ischaemic reaction to stress is less pronounced or may be nonexistent.

Therefore anti-anginal therapy may need to be withheld for 12 hours prior to dobutamine stress echocardiography.

When adding atropine at the highest titration level of dobutamine:

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.

4.6 Fertility, pregnancy and lactation

As there is 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 breast milk, so caution should be exercised. If treatment with dobutamine is required for the mother during lactation, breast feeding should be discontinued for the duration of treatment.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Very rare: $< 1/10,000$

Not known: cannot be estimated from the data available

Blood and lymphatic system disorders

Common: Eosinophilia, inhibition of thrombocyte aggregation (only when continuing infusion over a number of days).

Metabolism and nutrition disorders

Very rare: Hypokalaemia.

Nervous system disorders

Common: Headache.

Cardiac disorders / vascular disorders

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 blockers. Anginal pain, palpitations.

Uncommon: Ventricular tachycardia, ventricular fibrillation.

Very rare: Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest.

Not known: Decrease in pulmonary capillary pressure.

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.

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 second degree atrioventricular block, coronary vasospasms.

Hypertensive/hypotensive blood pressure decompensation, occurrence of intracavitary pressure gradients, palpitations.

Not known: Stress cardiomyopathy.

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.

Further undesirable effects

Restlessness, nausea, headache, paraesthesia, tremor, urinary urgency,

feeling of heat and anxiety, myoclonic spasm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose

Symptoms of overdose

Symptoms are generally caused by excessive stimulation of beta-receptors. Symptoms may include nausea, vomiting, anorexia, tremor, anxiety, palpitations, headache, anginal pain and unspecific chest pain. The positive inotropic and chronotropic cardiac effects may cause hypertension, supraventricular/ventricular arrhythmia and even ventricular fibrillation as well as myocardial ischaemia. Hypotension may occur due to peripheral vasodilatation.

Treatment of overdose

Dobutamine is metabolised rapidly and has a short duration of effect (half-life 2 - 3 minutes).

In case of overdose, administration of dobutamine should be terminated. If necessary, resuscitation procedures must be carried out immediately. Under conditions of intensive care, vital parameters must be monitored and corrected if necessary. Balanced levels of blood gases and serum electrolytes must be maintained.

Severe ventricular arrhythmias can be treated with administration of lidocaine or a beta blocker (e. g. propranolol).

Angina pectoris should be treated with a sublingually administered nitrate or possibly a short-acting, I.V. beta blocker (e.g. esmolol).

In case of a hypertensive reaction, dose reduction or termination of the infusion is usually sufficient.

With oral administration, the quantity absorbed from the mouth or gastrointestinal tract is unpredictable. In case of accidental oral administration, resorption may be reduced by administration of activated charcoal, which is often more effective than administration of emetics or performing gastric lavage.

The benefit of forced diuresis, peritoneal dialysis, haemodialysis or haemoperfusion via activated charcoal has not been demonstrated for cases of dobutamine overdosage.

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 administered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents

Dobutamine is a synthetic, sympathomimetic amine, structurally related to isoproterenol and dopamine, and is administered as racemate. The positive inotropic effect is primarily based on the

agonistic effect on cardiac β_1 -receptors but also on cardiac α_1 -receptors; which leads to increased contractility with an increase in stroke volume and cardiac output. Dobutamine also has an agonistic effect on peripheral β_2 -receptors and to a smaller extent on peripheral α_2 -receptors. In accordance with the pharmacological profile, positive chronotropic effects occur as well as effects on the peripheral vascular system. These however, are less pronounced than the effects of other catecholamines. The haemodynamic effects are dose-dependent. The cardiac output increases primarily due to an increase in the stroke volume; an increase in the heart rate is observed particularly with higher dosages. There is a reduction in left ventricular filling pressure and systemic vascular resistance. With higher doses, there is also a reduction in the pulmonary resistance. Occasionally an insignificant increase of the systemic vascular resistance can be observed. The volume increase due to an increase of the cardiac output is thought to be the reason for the blood pressure elevation. Dobutamine acts directly, independent from synaptic catecholamine concentrations, does not act at the dopamine receptor site, and – unlike dopamine – has no impact on the release of endogenous noradrenaline (norepinephrine).

There is a decrease of recovery time of sinus node and the A-V conduction time. Dobutamine may cause a tendency towards arrhythmia. When administered non-stop for more than 72 hours, tolerance phenomena were observed. Dobutamine impacts the functions of thrombocytes. Like all other inotropic substances, dobutamine increases myocardial oxygen demand. Via reduction of the pulmonary vascular resistance and the hyperperfusion even of hypoventilated alveolar areas (formation of a pulmonary

“Shunt”) a relatively reduced oxygen supply may occur in some cases. The increase in cardiac output and the resulting increase in coronary blood flow usually compensate these effects and cause – compared with other positive inotropic substances – a favourable oxygen supply/demand ratio.

Dobutamine is indicated for patients who require positive inotropic support in the treatment of cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures, especially when a low cardiac output is associated with raised pulmonary capillary pressure.

In cases of heart failure accompanied by acute or chronic myocardial ischaemia, administration should be performed in a manner to prevent considerable increase in heart rate or blood pressure; otherwise, particularly in patients with a relatively good ventricular function, increase of ischaemia cannot be excluded.

There are only limited data with regard to clinical outcome including long-term morbidity and mortality. So far, no data exists to support a beneficial long-term effect on morbidity and mortality.

Dobutamine has no direct dopaminergic effect on renal perfusion.

Paediatric population

Dobutamine 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 the heart rate and arterial blood pressure to increase more in children than in adults. Pulmonary wedge pressure may increase during

infusion of dobutamine 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

Onset of action is 1 - 2 minutes after the start of infusion; during continuing infusion, steady-state plasma levels are only reached after 10 - 12 minutes. Steady-state plasma levels increase dose-dependently linearly to

the infusion rate. Half-life is 2 - 3 minutes, distribution volume is 0.2 l/kg, plasma clearance is not dependent on cardiac output and is 2.4 l/min/m². Dobutamine is mainly metabolised in the tissue and liver. It is mainly metabolised to conjugated glucuronides as well as the pharmacologically inactive 3-O-methyldobutamine. The metabolites are mainly excreted in urine (more than 2/3 of the dose), and to a lesser extent in bile.

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.

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

Sodium metabisulfite.

Sodium chloride

Hydrochloric acid

Water for injections

6.2 Incompatibilities

Dobutamine solutions have proven to be 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,
- cephalozin 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:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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°C to 8°C unless preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the ampoules/vials in the outer carton in order to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container

Dobutamine 5 mg/ml (250 mg in 50 ml) ampoules made of colourless, neutral glass, type I Ph.Eur.

1, 5 and 10 ampoules with 50 ml solution for infusion.

Dobutamine 5 mg/ml (250 mg in 50 ml) vials made of colourless, neutral glass, type I Ph. Eur, with rubber stopper, Ph.Eur.

1, 5, 10 and 20 vials with 50 ml solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 5% glucose solution, 0.9% sodium chloride solution and 0.45% sodium chloride in 5% glucose solution.

Any unused solution should be discarded.

Note:

Solutions containing Dobutamine may have a pink colouration, which may become darker over time. This is due to a slight oxidation of the active substance. If storage instructions are observed (see also section 6.4 for Special storage instructions), there will not be a considerable loss in activity.

Immediately after opening the ampoule, there may be a sulfuric odour lasting for a short period. The quality of the medicinal product however is not impaired.

7.Manufactured in India by:

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