PATIENT INFORMATION LEAFLET

Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT DOBUTAMINE IS AND WHAT IT IS USED FOR

Dobutamine is a medicine which can help the pumping action of your heart.

It is a concentrated solution which is diluted to make a solution which can be given as a slow injection via a drip.

Dobutamine is used to treat heart failure associated with:

- Heart disease
- Heart attack
- Open heart surgery
- Weakened or abnormal heart muscle
- Low blood pressure after serious blood infections
- Low blood pressure due to a failing heart

Dobutamine may also be used to help your heart work if you are on a ventilator.

<u>Paediatric population</u>
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.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE DOBUTAMINE

Do not use dobutamine:

- if you know you are hypersensitive (allergic) to dobutamine or sulphites
- if you have an obstruction which is preventing blood flow into, or out of the heart
- if you have a very low blood volume
- if you suffer from chronic heart failure

Take Special Care

You should speak to your doctor:

- if you are pregnant
- if you are breast-feeding (you should discontinue breast-feeding whilst receiving dobutamine)
- if you get palpitations (fluttering heart beat)
- if you are asthmatic
- if you have kidney or liver problems
- if you are elderly
- if the patient is a child
- if you have had a heart attack
- if you have severe heart failure
- if you have very low blood pressure following heart problems

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including ones that are not prescribed for you.

In particular, tell your doctor if you are taking any of the following:

- propanolol or metoprolol ('beta blockers')
- "alpha-blocker" drugs which may be used in the treatment of high blood pressure or to increase urine flow if you have an enlarged prostate
- dipyridamole (angina medicine)
- cyclopropane and halothane (anesthetic drugs)
- sodium nitroprusside or nitroglycerin (peripheral vasodilators)
- vitamin B-1 also called thiamine (thiamine is essential to your cardiac health): dobutamine that contains sodium metabisulfite (an antioxidant) may react with thiamine and cause a reduction in the latter

PREGNANCY, BREAST-FEEDING AND FERTILITY

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

You will not be given dobutamine if you are pregnant unless your doctor thinks it is necessary.

Breastfeeding
You should discontinue breast-feeding whilst receiving dobutamine.

DRIVING AND USING MACHINES
The effect of Dobutamine on your ability to drive or use machinery is not predictable.

Important information about some of the ingredients of Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion
This medicine contains sodium metabisulphite, which may rarely cause hypersensitivity (severe allergy) reactions and bronchospasm (breathing difficulties).

Children
Increments in heart rate and blood pressure appear to be more frequent and intense in children than in adults. The new-born baby cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect (low blood pressure) seems to be more often observed in adult patients than in small children.

Accordingly, the use of dobutamine in children should be monitored closely.

3. HOW TO USE DOBUTAMINE

Your doctor will decide the correct dosage for you and how and when the injection will be given.

Dobutamine must be diluted before administration. It will be given to you intravenously (into a vein), preferably via a pump with a constant flow rate.

If you have the impression that the effect of dobutamine is too strong or too weak, consult your doctor or pharmacist.

The dose is usually in the range of 2.5 to 10 microgram per kilogram bodyweight per minute. This will be adjusted according to the results of measurement of your heart rate, blood pressure, cardiac output and urine output. In rare circumstances the dosage may be increased to 40 microgram per kilogram bodyweight per minute.

Use in Children
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. The required dose for children should be titrated in order to allow for the supposedly smaller “therapeutic width” in children.

Duration of Treatment
The infusion is given continuously, until your doctor decides to stop the treatment. You will not usually receive dobutamine for more than 3 days at a time.

As dobutamine will be given to you while you are in hospital it is unlikely that you will be given too much or too little. If you have any concerns please tell the doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, dobutamine can have side effects, although not everybody gets them.

If any of the following occur while you are given dobutamine, tell the doctor immediately:

- breathing difficulties
- chest pain
- irregular or increased heart beat
- severe allergic reaction- you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- raised blood pressure
- patients undergoing dobutamine stress echocardiography may also experience severely high blood pressure, dizziness, extreme fatigue and on occasion, heart attack

Possible side effects are listed according to the following categories:

- very common: may affect more than 1 in 10 people
- common: may affect up to 1 in 10 people
- uncommon: may affect up to 1 in 100 people
- rare: may affect up to 1 in 1,000 people
- very rare: may affect up to 1 in 10,000 people

Where no indication of frequency is provided below, this is because the frequency cannot be estimated from the available data.

Very common side effects:

- faster heartbeat
- fluttering heartbeat

Common side effects

- chest pain
- feeling sick or actually being sick
- headache
- rash
- fever
- increased white blood cell count (eosinophilia).
- difficulty in breathing or wheezing
- shortness of breath

Uncommon side effects

- abnormally fast and irregular heartbeat

Rare side effects

- swelling or pain at the site of infusion

Other reported undesirable effects of dobutamine are listed below:

- reduction in blood platelets, which increases the risk of bleeding or bruising
- tingling or numbness in the hands or feet
- mild cramping in the legs
- itching of the scalp
- serious allergic reaction (anaphylactic shock) which causes difficulty in breathing or dizziness
- raised blood pressure
- decreased level of potassium in the blood. You will be given regular blood tests to check this

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

HPRA Pharmacovilgance
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.hpra.ie/
Email: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE DOBUTAMINE

Keep out of the reach and sight of children.

Do not use dobutamine for injection after the expiry date printed on the vial label and pack.

The vials should not be stored above 25°C. Prepared infusions may be stored for up to 24 hours in a refrigerator at 2°C - 8°C.

If the solution has a slight pink colouration it will still be acceptable to use.

6. Further Information

What Dobutamine contains:

The active substance is dobutamine hydrochloride

The other ingredients are sodium metabisulphite (E223) and Water for injections

The medicine is presented in glass containers called vials.

Each ml (millilitre) of sodium contains 12.5 mg (milligrams) of dobutamine (as dobutamine hydrochloride).

The 20ml vial contains 1 x 20ml.

Marketing Authorisation Holder and Manufacturer:

Hospira UK Limited
Queensway, Royal Leamington Spa
Warwickshire, CV31 3RW
United Kingdom.

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Technical Leaflet

Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion

This is an extract from the Summary of Product Characteristics to assist in the administration of Dobutamine Concentrate for Solution for Infusion. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the full SmPC.

For intravenous infusion

Incompatibilities

Dobutamine 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 hydrochloride should not be mixed with other drugs in the same solution.

Dobutamine should not be used with drugs or diluents containing bisulphites or ethanol.

Preparation Instructions

Dobutamine Concentrate for Solution for Infusion is presented in vials containing 250 mg dobutamine (as dobutamine hydrochloride) in 20 ml and must be diluted to a final volume of at least 50 ml with the following IV infusion solutions:

Sodium Chloride Intravenous Infusion BP
5% Dextrose Intravenous Infusion BP

If diluting to 250 ml, 500 ml or 1000 ml, dilution will give a concentration for administration as follows:

250 ml contains 1000 micrograms/ml of dobutamine.
500 ml contains 500 micrograms/ml of dobutamine.
1000 ml contains 250 micrograms/ml of dobutamine.

Dosage and Administration

Administration

The concentration of dobutamine administered depends upon the dosage and fluid requirements of the individual patient. Concentrations of 5000 micrograms/ml have been used in fluid restricted patients but this concentration should not be exceeded. High concentrations of dobutamine should only be given with an infusion pump 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. An intravenous pump or other suitable apparatus should be used to control the flow rate in drops per minute.

Dosage
*Adults:*The usual rate 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. Up to 40 micrograms/kg/min may occasionally be required, but this is rare. Dobutamine infusions have been given for up to 72 hours without a decrease in effectiveness. It is recommended that treatment with dobutamine should be discontinued gradually.

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

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

Paediatric population: 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.

Warnings

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 increases atrioventricular conduction, patients with atrial flutter or fibrillation may develop a rapid ventricular response, and therefore should be digitalised prior to administration of dobutamine.

Experience with the use of dobutamine following acute myocardial infarction is limited. However 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 ischemia, cause anginal pain and ST segment elevation, therefore care should be exercised following myocardial infarction.

Dobutamine will not improve haemodynamics in most patients with mechanical obstruction affecting ventricular filling or outflow, or both.

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.

Minor vasoconstriction has been observed in patients treated with beta blocking drugs. This may occur due to the inotropic effect of dobutamine which stimulates cardiac beta-1 receptors and which is blocked by beta blockers. Conversely alpha adrenergic blockade may make the beta-1 and beta-2 effects apparent, resulting in tachycardia and vasodilation.

Before administration of dobutamine, hypovolaemia should be corrected with an appropriate plasma volume expander. The ECG, blood pressure and when possible, cardiac output and pulmonary wedge pressure should be monitored.

Like other drugs with ß2 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.

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 (E223) 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. Patients with bronchial asthma who are hypersensitive to sulfites may develop the following adverse effects: vomiting, diarrhoea, bronchoconstriction, altered states of consciousness and shock.

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, cardiac output, electrocardiography, urine flow rate, and blood and pulse pressure are available.

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.

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.

Possible complications associated with dobutamine stress echocardiogram include chest pain, severely high blood pressure, arrhythmias and heart attacks (see section 4).

No special measures are required in the event of extravasation, as no vasoconstriction or ischemia has been observed.

During continuous infusion (48-72 hours), the haemodynamic effect may be reduced, which indicates that higher doses are needed.

It is recommended that precautions be taken in patients with a history of severe ventricular arrhythmia.

Overdose
Overdosage has been reported rarely. 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 hydrochloride is generally short (half-life, approximately 2 minutes).

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

Forced diuresis, peritoneal dialysis, haemodialysis or charcoal haemoperfusion have not been established as beneficial.

If the product is ingested, unpredictable absorption may occur from the mouth and gastrointestinal tract.

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

Infusions must be aseptically prepared.

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C. Discard any unused product.

Solutions of dobutamine 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.

Marketing Authorisation Holder

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