Approved Professional Information for DOBUTAMINE 250 mg/20 ml FRESENIUS

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

DOBUTAMINE 250 mg/20 ml FRESENIUS concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 ml contains 250 mg dobutamine (as dobutamine hydrochloride).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly pink solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOBUTAMINE 250 mg/20 ml FRESENIUS is indicated in adults who require inotropic support in the treatment of heart failure due to cardiomyopathies (primary disease and hypocontractile function of the cardiac muscle), myocardial infarction or cardiac surgical procedures.

4.2 Posology and method of administration

For IV infusion once diluted.

Posology

The usual rate is 2,5 to 10 µg per kg body weight per minute, according to the patient's heart rate, blood pressure, cardiac output, and urine output. A range of 0,5 up to 40 µg per kg per minute has occasionally been required. It is recommended that treatment with DOBUTAMINE 250 mg/20 ml FRESENIUS should be discontinued gradually.

DOBUTAMINE 250 mg/20 ml FRESENIUS is administered by intravenous infusion as a dilute solution in:

- glucose 5 %
- glucose 5 % with sodium chloride 0,45 % or 0,9 %
- sodium chloride 0,9 %
- sodium lactate 1,85 %

Note: Do not add DOBUTAMINE 250 mg/20 ml FRESENIUS to 5 % sodium bicarbonate injection or any other strong alkaline solutions. DOBUTAMINE 250 mg/20 ml FRESENIUS should not be used other agents or diluents containing sodium metabisulphite and ethanol.

Method of administration

DOBUTAMINE 250 mg/20 ml FRESENIUS must be further diluted with sterile water for injection or 5 % dextrose injection to at least 50 ml prior to administration using the media as listed above.

Intravenous solutions for administration should be used within 24 hours. Discard any unused portion. Solutions containing DOBUTAMINE 250 mg/20 ml FRESENIUS may exhibit a slightly pink colour which, if present, will increase in time. This colour change is due to slight oxidation, but there is no significant loss of potency during the periods of reconstitution stated above.

The following table is suggested as a guide to rates of delivery:

Rates of delivery of three different concentrations* of DOBUTAMINE 250 mg/20 ml FRESENIUS to achieve required dosage			
Required dosage (µg/kg /min)	Rate of delivery (ml/kg/min) of the various concentrations of dobutamine		
	250 µg/ml**	500 µg/ml***	1 000 µg/ml****
0,5	0,002	0,001	0,0005
1,0	0,004	0,002	0,001
2,0	0,008	0,004	0,002
4,0	0,016	0,008	0,004
6,0	0,024	0,012	0,006
8,0	0,032	0,016	0,008
10,0	0,040	0,020	0,010
12,0	0,048	0,024	0,012
14,0	0,056	0,028	0,014

* Concentrations in excess of the highest presented here (1 000 µg/ml) may be administered in patients whose fluid intake must be restricted. Concentrations of up to 5 000 µg/ml have been given.

** One ampoule (250 mg) added to one litre of diluent.

*** Two ampoules (500 mg) added to one litre of diluent, or one ampoule (250 mg) added to 500 ml of diluent.

**** Four ampoules (1 000 mg or 1 g) added to one litre of diluent, or one ampoule (250 mg) added to 250 ml of diluent.

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, measurement of cardiac output.

4.3 Contraindications

- Hypersensitivity to dobutamine, sodium metabisulphite or to any of the other excipients (see section 6.1).
- Patients with marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis.
- Pregnancy, lactation and children.
- Phaeochromocytoma.

4.4 Special warnings and precautions for use

Dobutamine may precipitate or exacerbate ventricular ectopic activity; rarely, it has caused ventricular tachycardia or fibrillation.

DOBUTAMINE 250 mg/20 ml FRESENIUS acts primarily on β1 receptors and may produce hypertension, tachycardia and ectopic heartbeats.

Dysrhythmias may be precipitated; it is claimed that dobutamine causes a lower incidence of dysrhythmias compared with isoprenaline and dopamine. If rapid ventricular rates occur in the presence of obstructive coronary artery disease, ischaemia may be induced and worsened. Dobutamine may cause a marked increase in heart rate or systolic blood pressure. Reduction of dosage usually reverses these effects promptly.

Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation may be at risk of developing a rapid ventricular response.

If DOBUTAMINE 250 mg/20 ml FRESENIUS should cause serious ventricular dysrhythmia, uncontrolled by lidocaine, its infusion should be reduced or temporarily stopped. The infusion should be reduced or temporarily stopped if an undue rise in sinus rate or systolic blood

pressure occurs.

Particular care should be exercised when DOBUTAMINE 250 mg/20 ml FRESENIUS is used in patients with acute myocardial infarction, especially with widespread coronary artery disease, because any significant increases in heart rate that occur may intensify ischaemia and cause anginal pain and ST segment elevation.

DOBUTAMINE 250 mg/20 ml FRESENIUS does not improve haemodynamics in most patients with mechanical obstruction that hinders either ventricular filling or outflow, or both. Inotropic response may be inadequate in patients with markedly reduced ventricular compliance. Such conditions are present in cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis.

Minimal vasoconstriction has been observed, most notably in patients recently treated with β-blocking agents. Because the inotropic effect of DOBUTAMINE 250 mg/20 ml FRESENIUS stems from stimulation of cardiac β1 receptors, this effect is prevented by β-blocking agents. However, dobutamine has been shown to counteract the cardiodepressive effects of β-blockers. Conversely, adrenergic blockade may make the β1 and β2 effects apparent, resulting in tachycardia and vasodilatation.

During the administration of DOBUTAMINE 250 mg/20 ml FRESENIUS, as with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure and infusion rate should be monitored closely. When initiating therapy, electrocardiographic monitoring is advisable until a stable response is achieved.

Precipitous decreases in blood pressure have occasionally been described in association with DOBUTAMINE 250 mg/20 ml FRESENIUS therapy. Decreasing the dose or

discontinuing the infusion typically results in rapid return of blood pressure to base-line values, but rarely intervention may be required, and reversibility may not be immediate.

DOBUTAMINE 250 mg/20 ml FRESENIUS should be used with caution in the presence of severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70 mm Hg).

DOBUTAMINE 250 mg/20 ml FRESENIUS may exacerbate pre-existing tachycardia and hypertension; patients with arterial fibrillation should be given digoxin before dobutamine treatment to reduce the risk of enhanced atrioventricular conduction leading to ventricular fibrillation.

DOBUTAMINE 250 mg/20 ml FRESENIUS should be used with caution during anaesthesia with halogenated anaesthetics. The inotropic effects of dobutamine on the heart are reversed by concomitant administration of β-blockers. DOBUTAMINE 250 mg/20 ml FRESENIUS may be ineffective or may have a slight vasoconstricting effect in patients who have recently received β-blockers.

Hypovolaemia, if present, should be corrected with suitable volume expanders before patients receive DOBUTAMINE 250 mg/20 ml FRESENIUS.

If arterial blood pressure remains low or decreases progressively during administration of DOBUTAMINE 250 mg/20 ml FRESENIUS despite adequate ventricular filling pressure and cardiac output, consideration may be given to the concomitant use of a peripheral vasoconstrictor agent, such as dopamine or noradrenaline.

DOBUTAMINE 250 mg/20 ml FRESENIUS contains sodium metabisulphite

DOBUTAMINE 250 mg/20 ml FRESENIUS contains sodium metabisulphite, which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible patients. Sulphite sensitivity occurs more frequently in asthmatic than non-asthmatic people.

4.5 Interaction with other medicines and other forms of interaction

Halogenated anaesthetics

Although it is less likely than adrenaline to cause ventricular dysrhythmias, DOBUTAMINE 250 mg/20 ml FRESENIUS should be used with great caution during anaesthesia with cycloproprane, halothane and other halogenated anaesthetics.

Entacapone

The effects of DOBUTAMINE 250 mg/20 ml FRESENIUS may be enhanced by entacapone.

Beta-blockers

The inotropic effect of dobutamine, as in DOBUTAMINE 250 mg/20 ml FRESENIUS, stems from stimulation of cardiac β1 receptors; this effect is reversed by concomitant administration of β-blockers. Dobutamine has been shown to counteract the effect of β-blockers. In therapeutic doses, dobutamine has mild α1- and β2-agonist properties.

Concurrent administration of a non-selective β-blocker such as propranolol can result in elevated blood pressure, due to α-mediated vasoconstriction, and reflex bradycardia. β-blockers that also have α-blocking effects, such as carvedilol, may cause hypotension during concomitant use of dobutamine due to vasodilatation caused by β2 predominance (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety and/or efficacy has not been established in pregnancy and breastfeeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Since the half-life of dobutamine is only about 2 minutes, most adverse effects can be corrected by discontinuing or reducing the rate of infusion.

Blood and lymphatic system disorders

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

Immune system disorders

Frequency unknown: Hypersensitivity reactions, including rash, fever, eosinophilia and bronchospasm. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to sulphite sensitivity (see section 4.4).

Metabolism and nutrition disorders

Less frequent: Hypokalaemia.

Psychiatric disorders

Frequency unknown: Restlessness, feeling of heat and anxiety.

Nervous system disorders

Frequent: Headache.

Frequency unknown: Paraesthesia, tremor, myoclonic spasm. Myoclonus in patients suffering from severe renal failure.

Cardiac disorders

Frequent:	Increase of the heart rate by ≥ 30 beats/min. Anginal pain, non-specific chest pain, palpitations.
Less frequent:	Ventricular tachycardia or ectopic heartbeats, increased ventricular rate (in patients with pre-existing artrial fibrillation), ventricular fibrillation, bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest.
Frequency unknown:	Electrocardiogram ST segment elevation, decrease in pulmonary capillary pressure, eosinophilic myocarditis.

Vascular disorders

Frequent:	Blood pressure increase of ≥ 50 mm Hg (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 β-receptor blockers.
Less frequent:	Hypotension.
Frequency unknown:	Patients with pre-existing hypertension may exhibit an exaggerated pressor response.

Respiratory, thoracic and mediastinal disorders

Frequent:	Shortness of breath.

Gastrointestinal disorders

Frequency unknown: Nausea, vomiting.

Musculoskeletal and connective tissue disorders

Less frequent: Leg cramps.

Renal and urinary disorders

Frequency unknown: Urinary urgency.

Reporting of suspected adverse reactions

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of DOBUTAMINE 250 mg/20 ml FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of DOBUTAMINE 250 mg/20 ml FRESENIUS. Healthcare providers are asked to report any suspected adverse reactions via the **"Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Overdoses of dobutamine have been reported rarely. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath and anginal and non-specific chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachydysrhythmias, myocardial ischaemia and ventricular fibrillation.

Hypotension may result from vasodilatation.

Treatment

Treatment is symptomatic and supportive.

The duration of action of dobutamine is generally short (half-life approximately 2 minutes).

DOBUTAMINE 250 mg/20 ml FRESENIUS should be temporarily discontinued until the patient's condition stabilises. The patient should be monitored, and any appropriate resuscitative measures initiated promptly.

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

If DOBUTAMINE 250 mg/20 ml FRESENIUS is ingested, unpredictable absorption may occur from the mouth and gastrointestinal tract.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 6.1 Cardiac stimulants.

5.1 Pharmacodynamic properties

The pharmacological effects of dobutamine are due to direct interactions with both α- and β-adrenergic receptors; its actions do not appear to be a result of release of noradrenaline from sympathetic nerve endings.

Dobutamine possesses an asymmetric centre; the two enantiomeric forms are present in the racemic mixture that is used clinically. The effects of these two isomers that are mediated via β-adrenergic receptors are more straightforward. Dobutamine may have somewhat greater selectivity for β1 than for β2 receptors.

Cardiovascular effects:

Dobutamine has relatively more prominent inotropic than chronotropic effects on the heart compared with isoproterenol. At equivalent inotropic doses dobutamine enhances automaticity of the sinus node to a lesser extent than does isoproterenol. However, enhancement of atrioventricular and intraventricular conduction are similar for the two agents.

5.2 Pharmacokinetic properties

The onset of action is within one to two minutes. The peak effect of a particular dose may not be achieved for up to ten minutes.

The plasma half-life of dobutamine in humans is two minutes. The major routes of metabolism are methylation of the catechol and conjugation of dobutamine. In human urine the major excretion products are the conjugates of dobutamine and 3-*O*-methyl dobutamine. The 3-*O*-methyl derivative of dobutamine is inactive.
In patients with depressed cardiac function, both dobutamine and isoproterenol increases the cardiac contractility to a similar degree. Cardiac output is a function of stroke volume and heart rate. Dobutamine improves the cardiac output primarily by increasing stroke volume.

Systemic vascular resistance usually decreases at all dose levels of dobutamine. The pulse pressure is widened because stroke volume is increased. Dobutamine has little effect on mean arterial pressure in normotensive patients, but in patients who are hypotensive because of low output, mean arterial pressure rises with the increase in cardiac output. Because dobutamine acts by stimulating cardiac β1-receptors, cyclic AMP in cardiac tissues is increased.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 10 % *m/v* (for pH-adjustment)

Sodium hydroxide 10 % *m/v* (for pH-adjustment)

Sodium metabisulphite 0,02 % *m/v* (antioxidant)

Water for injection.

6.2 Incompatibilities

DOBUTAMINE 250 mg/20 ml FRESENIUS has been found to be physically incompatible with the following products:

Furosemide	Cephalothin
Hydrocortisone sodium succinate	Penicillin
Cefazolin	Sodium bicarbonate
Cefamandole nafate	Sodium ethacrynate

Sodium heparin.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

In combination with intravenous formulations it may be stored for 24 hours at or below 25 °C if dilution takes place under strict aseptic conditions. If dilution does not take place under strict aseptic conditions, the diluted solution is stable for a maximum of 24 hours at 2 – 8 °C (in a refrigerator), or 12 hours at or below 25 °C (room temperature), seen from a microbiological point of view.

Do not freeze.

6.5 Nature and contents of container

20 ml clear, colourless glass ampoule.

Pack sizes: 1 or 5 ampoules.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Midrand

1685

South Africa

8. REGISTRATION NUMBER

29/6.1/0345

9. DATE OF FIRST AUTHORISATION

20 September 1996

10. DATE OF REVISION OF THE TEXT

19 April 2022