1. **NAME OF THE MEDICINAL PRODUCT**

Dobutamin "Ebewe" 250mg – Concentrate for infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 vial (20ml) contains dobutamine hydrochloride equivalent to 250mg dobutamine.
For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

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

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Dobutamine is indicated for patients who require inotropic support due to

- acute heart failure and acute decompensation in chronic heart failure eg. as a result of acute myocardial infarction, cardiomyopathy, valvulopathy or heart surgery.
- low cardiac output primarily non-cardiac in origin, eg. as a result of septic shock or positive endexpiratory pressure (PEEP) ventilation.

Dobutamine may also be used for cardiac stress testing, as an alternative to exercise, in patients for whom routine exercise testing cannot be satisfactorily performed. This use of dobutamine 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.

4.2 Posology and method of administration

Dobutamin "Ebewe" is administered by continuous intravenous infusion. Prior administration Dobutamin "Ebewe" must be further diluted to at least 50ml (see 6.6.).
Dobutamin "Ebewe" should be administered by infusion pump to ensure a stable and regular delivery rate.
Dobutamin "Ebewe" should be given into a large vein, or preferable, directly into the central circulation to avoid local reactions (see 4.8. and 5.3.).
During the administration of Dobutamin "Ebewe" blood pressure, heart rate and rhythm, urine flow and infusion rate should be monitored continuously. Furthermore monitoring of cardiac output, central venous pressure, pulmonary artery pressure and pulmonary capillary wedge pressure is recommended.
Infusion rate and duration of therapy should be adjusted individually to the patient's response.
Adults:
Most patients will respond to doses between 2.5 and 10µg/kg/min. In rare cases doses up to 40µg/kg/min have been administered.
Children:
In children infusion rates between 0.5 and 20µg/kg/min have been administered.
There are some differences in haemodynamic response compared with adults. There is evidence that the minimally effective infusion rate is higher and the maximally tolerated infusion rate is lower than in adults; therefore infusion rate should be adjusted very carefully (see 4.4).
Continuous infusion over a period greater than 72 hours may lead to tolerance.
To avoid rebound effects at the end of administration it is recommended to decrease the dosage of dobutamine gradually rather than abruptly.

Administration by infusion pump and a 50ml injection syringe (eg. Perfusor®)
The content of 1 vial is diluted to 50ml (drug concentration 5000µg/ml)

	values in ml/h (ml/min)		
	weight of the patient		
	50 kg	70 kg	90 kg
low dose (2.5µg/kg/min)	1.5 (0.025)	2.1 (0.035)	2.7 (0.045)
intermediate dose (5µg/kg/min)	3.0 (0.05)	4.2 (0.07)	5.4 (0.09)
high dose (10µg/kg/min)	6.0 (0.1)	8.4 (0.14)	10.8 (0.18)

Administration by infusion pump (e.g. Infusomat®)
The content of 1 vial is diluted to 500ml (drug concentration 500µg/ml)

	values in ml/h		
	weight of the patient		
	50 kg	70 kg	90 kg
low dose (2.5µg/kg/min)	15 (5)	21 (7)	27 (9)
intermediate dose (5µg/kg/min)	30 (10)	42 (14)	54 (18)
high dose (10µg/kg/min)	60 (20)	84 (28)	108 (36)

Cardiac stress testing: When used as an alternative to exercise for cardiac stress testing, the recommended dose is an incremental increase of 5 micrograms/kg/min from 5 up to 20 micrograms/kg/min, each dose being infused for 8 minutes. Continuous ECG monitoring is essential and the infusion terminated in the event of >3mm 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 220mm Hg or any side effects occur see "Undesirable effects".

4.3 Contraindications

Hypersensitivity to dobutamine hydrochloride or sodium pyrosulfite (esp. hypersensitivity of asthmatic patients to sulfite).
Mechanical obstruction of ventricular filling or ejection (eg. severe aortic stenosis, obstructive hypertrophic cardiomyopathy, cardiac tamponade, constrictive pericarditis).
Sustained tachyarrhythmia, which does not respond to antiarrhythmic treatment.

4.4 Special warnings and special precautions for use

Warnings
Hypovolaemia:
Prior initiation of therapy hypovolaemia should be corrected. Volume should also be maintained throughout treatment.
Atrial flutter, atrial fibrillation:
Supraventricular tachyarrhythmia may occur since dobutamine facilitates atrioventricular conduction. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior administration of dobutamine.
Ventricular ectopic activity, ventricular arrhythmia:
Condition may be exacerbated.
Myocardial infarction:
Excessive doses of dobutamine may intensify ischaemia by increasing myocardial oxygen demands.
Phaeochromocytoma:
Severe hypertension may occur.
Preexisting hypertension:
There may be an increased risk of a hypertensive response.
Hyperthyroidism:
Sensitivity to sympathomimetics may be increased.
Hypokalaemia:
Dobutamine may increase the risk of hypokalaemia. Preexisting hypokalaemia should be corrected. During administration of dobutamine monitoring of serum potassium concentration is recommended.
Administration in children:
The nature and extent of some haemodynamic effects of dobutamine may be different in children. An increase in arterial pressure appears to be more frequent and more intense. Pulmonary capillary pressure, lowered by dobutamine in adults, may not be reduced in children, but may be raised, particularly in children under one year of age. Therefore administration must be monitored very carefully.
Precautions
Dobutamin "Ebewe" should be administered only by physicians with cardiological experience.
During the administration of Dobutamin "Ebewe" blood pressure, heart rate and rhythm, urine flow and infusion rate should be monitored continuously. Furthermore monitoring of cardiac output, central venous pressure, pulmonary artery pressure and pulmonary capillary wedge pressure is recommended.
If tachycardia or an undue increase in systolic blood pressure occurs of if severe hypotension is present (mean arterial pressure <70mm Hg) or if an arrhythmia is precipitated, the dose of dobutamine should be reduced or the drug should be discontinued temporarily.
The infusion volume should be adjusted to the fluid requirements of the patient.
When arterial blood pressure remains low or is reduced despite sufficient ventricular filling pressure and cardiac output, a vasoconstrictive substance (eg. dopamine, norepinephrine) may be administered concomitantly.
Continuous infusion over a period greater than 72 hours may lead to tolerance.
The use of dobutamine as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, bundle branch block, valvular heart disease, aortic outflow obstruction, or any cardiac condition that could make them unsuitable for exercise stress testing.

4.5 Interaction with other medicinal products and other forms of interaction

Precautions:
Volatile anesthetics (esp. cyclopropan, halothan):
There may be an increased risk of ventricular arrhythmias.
Beta-adrenergic blocking agents:
There may be a mutual inhibition of therapeutic effects. Unopposed alpha-receptor mediated activity of dobutamine may lead to vasoconstriction and increase of arterial blood pressure.
Alpha-adrenergic blocking agents:
There may be a mutual inhibition of therapeutic effects. Unopposed beta-receptor mediated activity of dobutamine may increase tachycardia and vasodilation.
MAO-inhibitors, guanethidine, Rauwolfia alkaloids:
The sympathomimetic effect of dobutamine may be increased. The concomitant administration of MAO-inhibitors should be avoided.
Taken into account:
Insulin:
There may be a reduced blood sugar lowering effect in diabetics.
ACE-inhibitors:
There may be an increase of cardiac output. Concomitantly administered doses greater than 10µg/d/kg/min may lead to an increase of myocardial oxygen demands; cases of chest pain and arrhythmia have been reported.
Dopamine:
Systemic arterial blood pressure may increase, renal function may be improved.
Venodilators (eg. nitrates, sodium nitroprusside):
There may be synergistic effects on haemodynamic parameters (ventricular filling pressure, cardiac output, pulmonary capillary wedge pressure).

4.6 Pregnancy and lactation

Reproduction studies revealed no evidence of fertility impairment, teratogenicity or harm to the fetus. There is not sufficient experience in humans. Dobutamine should therefore only be administered when urgently needed.
It is not known, whether dobutamine is distributed into breast milk. When administration of dobutamine is considered necessary ablactation is recommended.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Systemic:
Increase of heart rate (5–15 beats/min) and systolic blood pressure (10–20mmHg), more intense in approximately 10% of patients and in children; increase of pulmonary capillary wedge pressure in children under one year of age.
Hypotension, ventricular arrhythmia (esp. premature beats, in rare cases tachycardia, fibrillation), supraventricular tachyarrhythmia in patients with atrial flutter or fibrillation.

Nausea, headache, angina, chest pain, palpitation, dyspnea, reduction of serum potassium concentration/hypokalaemia.
Hypersensitivity reactions (pruritus, exanthema, fever, chills, eosinophilia, bronchospasm).
In rare cases urinary urgency, peripheral ischemia, tremor and petechial bleedings (possibly due to inhibition of platelet aggregation).
In single cases hypersensitivity reactions due to sulfite may occur, esp. in asthmatic patients (eg. nausea, diarrhoea, dyspnea, acute asthmatic attack, impaired consciousness, shock). These reactions may vary and may be life threatening.
Injection site:
Phlebitis, paravenous inflammation (following inadvertant infiltration).
In single cases dermal necrosis following extravasation.

4.9 Overdose
Symptoms:
Inappetence, nausea, vomiting, tremor, anxiety, palpitations, headache, dyspnea, angina, chest pain, hypertension, tachyarrhythmia, myocardial ischemia, ventricular fibrillation, hypotension.
Management:
Reduction of infusion rate, discontinuation of infusion.
Symptomatical therapy, if needed (eg. lidocaine or beta adrenergic blocking agents in cases of severe ventricular arrhythmia).
When inadvertant ingestion occurs, administration of activated charcoal may be considered.
Forced diuresis, peritoneal dialysis, haemodialysis and haemoperfusion have not been proved useful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC Code: C01C A07 Pharmacotherapeutical class: cardial stimulants
Dobutamine is a synthetic sympathomimetic amine. The pharmacological actions of the administered racemate result from different affinities of the (+) and (-) enantiomer for α- and ß-adrenergic receptors: (-) dobutamine is a potent agonist at α_1-adrenergic receptors, (+) dobutamine is an α_1-adrenergic antagonist and may attenuate the effect of the (-) enantiomer. Both enantiomers are agonists at ß-adrenergic receptors, the (+) enantiomer with tenfold higher potency. Dobutamine has low selectivity for $ß_1$-adrenergic receptors. There is no release of endogenous norepinephrine.
Due to stimulation of $ß_1$- and α_1-adrenergic receptors of the heart dobutamine increases myocardial contractility and stroke volume, resulting in increased cardiac output and reduction of elevated ventricular filling pressure (preload reduction). Coronary blood flow and myocardial oxygen consumption are usually increased because of increased cardiac output.
Dobutamine has little effect on systemic vascular resistance, and systolic and pulse pressure may remain unchanged or be increased because of increased cardiac output.
However, in septic patients with decreased systemic resistance, dobutamine may lower blood pressure without increasing cardiac output.
Dobutamine facilitates atrioventricular node conduction. At appropriate doses, an increase in heart rate does not usually occur, but high doses have a chronotropic effect.
Renal blood flow and urine output may be improved as a result of increased cardiac output.
Onset of action occurs within 1-2 minutes; however up to 10 minutes may be required when infusion rate is low. When the infusion has been discontinued, duration of action is less than 5 minutes.

5.2 Pharmacokinetic properties
Dobutamine has a plasma elimination half life of about 2-3 min. Volume of distribution is 0.2 L/kg, plasma clearance 2.4 L/min/m². Dobutamine is metabolised by conjugation and methylation mainly to glucuronides and 3-O-methyl dobutamine. The metabolites are eliminated by the urinary (2/3) and the biliary routes.

5.3 Preclinical safety data
As far as available preclinical data reveal no special hazards for humans based on studies of repeated dose toxicity, genotoxity and toxicity to reproduction.
Local tolerance:
Dobutamin "Ebewe" revealed good local compliance in rabbits after i.v. infusion at an infusion rate of 166µg/kg/min. Following application made in error (i.a., p.v., i.m. and s.c.) Dobutamin "Ebewe" revealed mild to moderate intolerance reactions above all following p.v., i.m. and s.c. injection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium metabisulfite 0.1125mg/ml (equivalent to 0.08mg SO_2/ml), hydrochloric acid, nitrogen, water for injection.

6.2 Incompatibilities
Dobutamin "Ebewe" must not be mixed with other preparations except the solutions stated in 6.6.
Dobutamin "Ebewe" is incompatible with alkaline solutions (eg. 5% sodium bicarbonat), solutions containing both sodium bisulfite and ethanol, furosemide, etacryn acid (incl. sodium salt), hydrocortisone sodium succinate, cefazolin sodium cefamandole sodium, cephalothin sodium, penicillin G, heparin (incl. salts), phenytoin sodium, human insulin, diazepam, aminophylline.
Sulfite is a highly reactive substance and may lead to further incompatibility reactions.

6.3 Shelf life
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 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.
The shelf-life of the medicinal product as packaged for sale is 18 months.

6.4 Special precautions for storage
Do not store above 25°C.
Keep container in the outer carton, in order to protect from light.

6.5 Nature and contents of container
Amber glass vial with rubber stopper.

20ml vial, packed in a carton.

6.6 Instructions for use and handling
Prior administration Dobutamin "Ebewe" must be further diluted to at least 50ml in 5% glucose or 0.9% saline.
For administration by infusion pump (e.g. Infusomat®) the content of 1 vial is diluted to 500ml (drug concentration 500µg/ml).
For administration by infusion pump and a 50ml injection syringe (eg. Perfusor®) the content of 1 vial is diluted to 50ml (drug concentration 5000µg/ml).
Solutions diluted for infusion should be prepared immediately before administration and should be used within 24 hours. They should be protected from direct light and UV irradiation.
Only clear and colourless solutions should be used.
Pink discolouration of dobutamine solutions indicates slight oxidation of the active substance, but there is no significant loss of potency if administered within the recommend time periods and precautions for storage are observed (see 6.4.).
Solutions diluted for infusion must not be mixed with other medication (see 6.2.).
When other intravenous agents are administered concomitantly, a separate intravenous line should be used. Otherwise bypass compatibility must be tested prior administration.
Only for single use.

7. MANUFACTURER
EBEWE Pharma Ges.m.b.H. Nfg.KG, A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT
June 2002