SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIOZAC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 20 ml contains:

Active ingredient:
Dobutamine hydrochloride 280.28 mg
(Equivalent to Dobutamine 250.0 mg)

(each ml contains 12.5 mg of Dobutamine)

Excipient with known effect:
Sodium metabisulphite 4.4 mg

For the full list of the excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sterile concentrated solution for intravenous infusion.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Dobutamine is indicated for patients who require a positive inotropic support in the short term treatment of adults with 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 pressure.

Note
In case of cardiogenic shock characterized by cardiac failure and severe hypotension and in case of septic shock dopamine is the drug of first-choice after correction of possible hypovolemia.
In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutamine 12.5 mg/ml.

4.2 Posology and method of administration

Just before administration Dobutamine concentrate for solution for infusion **must** be further diluted to **at least 50 ml** prior to administration in a container for intravenous use and according to the table below with one of the intravenous solutions listed in section 6.6.
The concentration used depends on the dosage and fluid requirements of the patient. The dilution should not be more concentrated than 5 mg/ml (5,000 µg/ml). Most patients will respond satisfactorily to doses from 2.5 to 10 µg/kg/min. Occasionally, however, a dose as low as 0.5 µg/kg/min will be effective. Rarely, a dose as high as 40 µg/kg/min has been required.

The table below is a directive for the rate of infusion:

Drug Delivery Rate	**Infusion Delivery Rate (ml/kg/min)**			
(µg/kg/min)	250 µg/ml*	500 µg/ml**	1000 µg/ml***	5000 µg/ml****
0.5	0.002	0.001	0.0005	0.0001
1.0	0.004	0.002	0.0010	0.0002
2.5	0.010	0.005	0.0025	0.0005
5.0	0.020	0.010	0.0050	0.0010
7.5	0.030	0.015	0.0075	0.0015
10.0	0.040	0.020	0.0100	0.0020

12.5	0.050	0.025	0.0125	0.0025
15.0	0.060	0.030	0.0150	0.0030

* 250 mg of Dobutamine (1 vial) added to 1 liter of diluent.
** 500 mg of Dobutamine (2 vials) added to 1 liter of diluent or 250 mg (1 vial) added to 500 ml of diluent.
*** 1000 mg Dobutamine (4 vials) added to 1 liter of diluent or 250 mg (1 vial) added to 250 ml of diluent.
**** 250 mg of Dobutamine (1 vial) added to 50 ml of diluent. This dilution can be used in patients with restricted fluid intake.

The rate of administration and the duration of the therapy must be individualized to the patient's requirements and response as determined by heart rate, blood pressure, urine flow, and, whenever possible, measurement of cardiac output.
Because of the development of partial tolerance with continuous infusions of Dobutamine for 72 hours or more, higher doses may be required to maintain the same effects.
Rather than abruptly discontinuing the duration of therapy with Dobutamine, it is often advisable to decrease the dosage gradually.

4.3 Contraindications

Hypersensitivity to Dobutamine hydrochloride or to any of the excipients listed in section 6.1.
MIOZAC solution is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients with ascertained hypersensitivity to the product.

4.4 Special warnings and precautions for use

During the administration of MIOZAC solution, as with any other adrenergic agent, the ECG and blood pressure must be continuously monitored.
In addition, whenever possible and for the purpose of a safe and effective infusion of MIOZAC solution, pulmonary capillary pressure and cardiac output should be monitored.

Hypovolemia must be appropriately corrected before starting treatment with MIOZAC solution.
Animal studies indicate that MIOZAC solution may be ineffective if ß-blocking drugs have been recently administered.
In this case, the peripheral vascular resistance can increase.

No improvement can be observed in the presence of marked mechanical obstruction, such as in severe aortic valve stenosis.

Dobutamine, likewise other ß2-agonists, can cause a modest reduction in serum potassium without reaching or rarely reaching, hypokalaemia levels. It is therefore recommended to monitor potassium during therapy with MIOZAC solution.

Stress cardiomyopathy (Takotsubo syndrome) is a possible severe complication of the use of dobutamine during stress echocardiography (see section 4.8). The administration of dobutamine for stress echocardiography should be only undertaken by a physician experienced with the procedure. The physician should be vigilant during the test and the recovery period and be prepared for appropriate therapeutic intervention during the test. In the event of stress cardiomyopathy (Takotsubo syndrome) dobutamine should be stopped immediately.

Use after acute myocardial infarction
Clinical experience with MIOZAC solution after acute myocardial infarction is insufficient to establish the safety of the drug for this use.
It is known that any pharmacological agent capable of increasing the contractile force of the heart and its frequency can cause an increase in the infarcted area, but it is not known whether this can also occur with Dobutamine.

Increase in heart rate and arterial pressure
MIOZAC solution may provoke a considerable increase in heart rate or arterial pressure, especially systolic.
In clinical studies, approximately 10% of patients experienced rhythm increases of 30 beats/min or more, and approximately 7.5% experienced increases in systolic blood pressure of 50 mmHg or more. All these effects may generally be decreased or eliminated with the decrease in the dosage.

Because Dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing a rapid ventricular response. Previously hypertensive patients are at the highest risk of an exaggerated blood pressure response.

Ectopic activity
MIOZAC solution can precipitate or aggravate ectopic ventricular activity but has rarely caused ventricular tachycardia.

Hypersensitivity
Hypersensitivity reactions associated with the administration of MIOZAC solution have occasionally been reported, including skin rash, fever, eosinophilia, and bronchospasm.

Important information about some of the ingredients:
The product contains sodium metabisulphite: this substance may rarely cause severe hypersensitivity reactions and bronchospasm.

Each vial contains less than 1 mmol (23 mg) of sodium, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There were no drug interactions between MIOZAC solution and other drugs such as digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl nitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and phenacetin.

Preliminary studies have shown that the concomitant use of dobutamine and nitroprusside causes an increase in cardiac output and generally a decrease in pulmonary capillary pressure, greater than that induced by the two drugs used individually.

4.6 Fertility, pregnancy and lactation

Reproduction studies performed in rats and rabbits did not reveal any effects on fertility, fetal harm or teratogenic effects due to dobutamine.

The drug has not been administered to pregnant women and should therefore only be used in these cases when the potential benefits clearly go over the potential risks to the foetus and under direct medical supervision.

Paediatric use
The safety and efficacy of MIOZAC solution for use in paediatrics have not been studied.

4.7 Effects on the ability to drive and use machines

There is no data available to establish the effect of the medicine on the ability to drive and use machines.

4.8 Adverse effects

Increase in heart rate, arterial pressure and ectopic ventricular activity
In the majority of patients, an increase of 10-20 mmHg in systolic pressure and an increase in heart rate of 5-15 beats per minute have been noticed. In about 5% of patients, there was an increase in ventricular extrasystoles during the infusion. These effects are dose-related.

Arterial hypotension
Occasionally rapid falls in blood pressure have been reported during the administration of dobutamine. The dose reduction and interruption of the infusion quickly bring blood pressure values back to pre-infusion levels.

Reactions at the injection site
A phlebitis has occasionally been reported. Local inflammations have been described following extravasation resulting from improperly performed manoeuvres.

Uncommon side effects

In 1-3% of the patients, the following side effects were noted: nausea, headache, anginal pain or non-specific chest pains, palpitations and dyspnoea.

Cardiac disorders with a not known frequency:
Stress cardiomyopathy (Takotsubo syndrome) (read the section 4.4)

Long-term treatment safety
The side effects for infusion up to 72 hours were not different from those ones observed in short-term treatments.

Laboratory tests
MIOZAC, like other catecholamines, can induce a modest reduction in potassium, rarely to hypokalemia levels (see section 4.4).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose
Cases of dobutamine overdose have been reported rarely.

Signs and symptoms
The toxic phenomena of dobutamine are generally due to an overstimulation of the ß-cardiac receptors. The duration of action of dobutamine is generally short (T½ - 2 minutes) due to the rapid metabolization by catechol-O-methyltransferase. Symptoms of toxicity include anorexia, nausea and vomiting, tremors, anxiety, palpitations, headache, dyspnoea, anginal and non-specific chest pains. The positive inotropic and chronotropic effects of dobutamine on myocardial may cause hypertension, tachyarrhythmias, myocardial ischemia and ventricular fibrillation. Hypotension can result in vasodilation.
If the product is ingested orally, any absorption from the oral and intestinal mucosa is unpredictable.

Treatment
The initial action consists in suspending the administration of dobutamine, establishing the patency of the airways and ensuring oxygenation and ventilation. Promptly implement the measures of resuscitation.
The severe ventricular tachyarrhythmia can be successfully treated with propanol or lidocaine. Hypertension generally responds to dose reduction or discontinuation of therapy.

If necessary, carefully monitor and maintain, within acceptable limits, the vital signs, blood gases, serum electrolytes, etc. Drug absorption by the gastrointestinal tract can be reduced by activated charcoal, which is often more effective than induction of vomit or gastric lavage. Therefore, consider the administration of activated charcoal in addition or instead of gastric lavage. The repeated administration of charcoal can accelerate the elimination of some drugs which have previously been taken.

When performing gastric emptying manoeuvres or activated charcoal administration, check the integrity of the respiratory tract.

Forced diuresis, peritoneal dialysis, hemodialysis, and charcoal hemoperfusion have not been shown to be beneficial in cases of dobutamine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

MIOZAC solution is a direct-acting inotropic agent whose primary activity consists of stimulation of the ß1 receptors of the heart, while it has relatively modest chronotropic, hypertensive, arrhythmogenic and vasodilatory effects.

Unlike dopamine, it does not induce endogenous norepinephrine secretion.
In laboratory animals, for a given inotropic effect, dobutamine causes a lower increase in heart rate and a lower decrease in peripheral vascular resistance than isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol induce the same increase in cardiac output. The dobutamine increases the systolic output without significantly increasing heart rate (however, tachycardia has occasionally been observed). On the contrary, isoproterenol increases cardiac output essentially with an increase in heart rate, while systolic output varies little or decreases.

The differential pressure increases with dobutamine as a consequence of the increase in systolic output. Dobutamine has a minimal effect on mean arterial pressure in normotensive patients, while in patients with low output syndrome the mean arterial pressure increases with the increasing of a cardiac output.

A facilitation of atrioventricular conduction has been observed in human electrophysiology studies and in patients with atrial fibrillation.

The systemic vascular resistance, after the administration of dobutamine, generally decreases. In some cases, it is possible to observe a minimal degree of vasoconstriction. Most dobutamine experiences have been carried out in a short term, up to a few hours.

In the limited number of patients who were studied for 24, 48 and 72 hours, in some of them the increase in cardiac output persisted, while in others it returned to baseline values.

5.2 Pharmacokinetic properties

The start of the activity of MIOZAC solution occurs in one or two minutes: to obtain the maximum effect at a certain infusion frequency, on the other hand, it can take up to ten minutes. The plasma half-life of dobutamine in humans is two minutes. The main metabolic pathways are methylation and conjugation of the catechol group.

In human urine, the main excreted products consist of dobutamine and 3-0-methyldobutamine conjugates. the 3-0-methyl derivative of dobutamine is inactive.

Changes in the synaptic concentrations of catecholamines using reserpine or tricyclic antidepressants do not alter the effects of dobutamine in animals, this indicates that the effects of dobutamine are not dependent on pre-synaptic mechanisms.

5.3 Preclinical safety data

Studies on the mutagenic and carcinogenic potential of dobutamine have not been performed. Reproduction studies in rats and rabbits (at maternally toxic doses) revealed impairment of implantation and did not reveal any adverse effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite
Water for injections
Hydrochloric acid
Sodium Hydroxide

6.2 Incompatibilities

Do not dilute MIOZAC with 5% sodium bicarbonate solutions or with other solutions strongly alkaline. MIOZAC should not be used with other substances containing sodium metabisulfite and ethanol.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
For shelf life after dilution see clause 6.6.

6.4 Special precautions for storage
Store at a temperature below 25 °C and protected from light.

6.5 Nature and contents of container
The product is packaged in type I colorless and transparent glass vials, closed with rubber stopper and sealed with aluminum cap with flip-off made of plastic.

6.6 Special precautions for disposal and other handling
Dobutamine concentrate solution **must** be further diluted to **at least 50 ml** prior to administration in an i.v. container with one of the intravenous solutions listed below:

- 5% Dextrose
- 5% Dextrose + 0.45% Sodium chloride
- 5% Dextrose + 0.9% Sodium chloride
- 10% Dextrose
- Isolyte M + 5% Dextrose
- Ringer Lactate
- 5% Dextrose + Ringer Lactate
- 20% Osmitrol in water
- 0.9% Sodium Chloride
- Sodium Lactate
- Normosol M in D5W

Solutions containing MIOZAC, may turn pink, which may increase in intensity over time.
This colour change is due to a slight oxidation of the drug but, over the recommended time of administration, there is no significant loss of potency.

The diluted solution must be used within 24 hours, stored at a temperature below 25°C, but from a microbiological point of view, the product should be used immediately after dilution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER and importer
RAZ PHARMACEUTICS LTD., 31 Gesher haetz Street, Emek Hefer Industrial Park, Israel.

8. MARKETING AUTHORISATION NUMBER
174-22-36662-99

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