MIOZAC 250 mg/20 ml Solution for infusion
(Dobutamine Hydrochloride)

COMPOSITION
Each vial contains:

Active ingredient:
Dobutamine hydrochloride 280,28 mg equivalent to Dobutamine 250,0 mg

Excipients:
Sodium metabisulphite 4,4 mg
Water for injection q.s. to 20ml

PHARMACEUTICAL FORM AND CONTENT
Solution for infusion. Vial of 250 mg/20 ml

PHARMACOTHERAPEUTIC CATEGORY
Cardiac stimulators (adrenergic and dopaminergic)

MARKETING LICENCE HOLDER, MANUFACTURER AND FINISHED PRODUCT RELEASER:
FISIOPHARMA SRL, Nucleo Industriale, 84020 Palomonte (SA), ITALY

THERAPEUTIC INDICATIONS
MIOZAC solution, is indicated in cases in which a rapid support to the myocardical inotropic activity is required. It is used in the management of congestive heart failure in adults, associated with organic heart disease, cardiogenic or septic shock, myocardial infarction and cardiac surgery. In subjects affected by atrial fibrillation, prior to introduce Miozac therapy a digital preparation must be employed.

CONTRAINDICATIONS
MIOZAC solution is contraindicated in subjects hypersensitive to the drug or to its components or in subjects affected by hypertrophic subaortic stenosis.

PRECAUTIONS
Patients with atrial fibrillation should be given a cardiac glycoside prior to be treated with Miozac solution.

- In the course of administration of Miozac solution as in the case of all other adrenergic agents, the ECG, arterial pressure, lung capillary pressure, and cardiac output should be continuously monitored.
  Prior to the treatment with Miozac solution a possible hypovolemic state should be adjusted by plasma appropriate substituting solutions.
- Dobutamine, likewise other $ß_2$- agonists, may provoke a modest reduction of serous potassium rarely reaching the hypopotassemia levels. However, the hypopotassemia monitoring is recommended

CARCINOGENESIS, MUTAGENESIS AND FERTILITY ALTERATIONS
Reproduction studies carried out in rats and rabbits haven't revealed any negative effects on fertility or damages of foetus.

USES IN PREGNANCY AND NURSING
A pregnant woman should be treated with Miozac if only effectively necessary and under direct control of a physician

INTERACTIONS WITH OTHER DRUGS
If given in combination with sodium nitroprusside Miozac may provoke cardiac output increase and generally lung capillary pressure decrease stronger than that induced by a drug itself.
Clinical studies report no interaction disturbances of Miozac and other drugs such as digital medicines, furosemide, trinitrine, dinitrate isosorbide, morphine, atropine, heparin, protamine, potassium chloride, folic acid and paracetamol.
Studies conducted in animals have demonstrated that Miozac may be ineffective in case of subjects previously treated by ß-blocking drugs because the peripheral vascular resistance may increase.

SPECIAL WARNINGS

- Miozac solution may provoke a considerable increase of heart rate or arterial pressure particularly the stroke volume. In approx. 10% of subjects the heart rate of 30 pulsations or more per a minute has been registered and in approx. 7,5% an increase of stroke volume of 50 mmHg or more has been reported.
  All these effects can generally be decreased or eliminated if a dosage decreases.
  Since Miozac facilitates atrioventricular conduction, a rapid ventricular response has not been observed in subjects affected by atrial fibrillation. A risk of an exaggerated pressure response has been observed in subjects with existing arterial hypertension.
  In case of marked mechanic obstructions of a left ventricular flow as in case of serious aortic valvular stenosis, signs of improvement may not be observed.
- Miozac solution may precipitate or increase an ectopic ventricular activity and rarely provoke ventricular tachycardia.
- Presumable natural allergic reactions have been rarely observed such as cutaneous rush, fever, eosinophilia and bronchospasm.
- Miozac solution contains sodium bisulphite which in sensible and particularly in asthmatic subjects may provoke allergic reactions and serious asthmatic attacks.

Negative effects on ability of driving and handling of machinery haven't been reported.

POST-INFARCTION TREATMENT
Clinical studies are insufficient to stabilise safety of administration of Miozac in the post-infarction period. Administration of an agent increasing contractile force and heart rate and having as consequence the possibility to increase infarction area may have certain risks. However, it hasn't been reported that Miozac might provoke such effects.

Sports performance
Use of the drug without therapeutic necessity constitutes dope. It may determine doping effects causing even for therapeutic doses positive results to anti-doping tests.

POSOLOGY AND METHOD OF ADMINISTRATION
Rate of administration required to increase cardiac output ranges from 2,5 to 10 mcg/kg/min.
To obtain a desired effect, MIOZAC has been rarely given by rate up to 40 mcg/kg/min (see the table below).

INFUSION RATE (ml/kg/min) FOR CONCENTRATIONS
of 250, 500 and 1000 mg / L

ADMINISTRATION RATE (mcg/Kg/min)	INFUSION RATE		
	250mg\l (ml/Kg/min)	500mg\l (ml/Kg/min)	1000 mg\l (ml/Kg/min)
2,5	0,01	0,005	0,0025
5	0,02	0,010	0,0050
7,5	0.03	0,015	0,0075

10	0,04	0,020	0,0100
12,5	0,05	0,025	0,0125
15	0.06	0,030	0.0150

Administration rate and duration of treatment should be adjusted with respect to the patient's response, determined from the cardiac frequency, the presence of ectopic activity, the arterial pressure, the urine output and, when possible, from the measurement of the pulmonary capillary pressure and from the cardiac capacity.
Concentrations up to 250 mg/50 ml have been given in the man.
Total volume of liquids to be administered to a patient must be compatible with hydrous requirements.

Solubility and stability

Note: MIOZAC solution is not compatible with alkaline solutions and must not be mixed with a 5% sodium bicarbonate solutions.
MIOZAC solution can't be used with other agents or solutions containing sodium bisulphite and ethanol.

Reconstituted substance and stability:
At the moment of administration, MIOZAC solution must be further diluted in the vial at least up to 50 ml, using one of the solvents indicated below:

Dextrose at 5%	for injection
Dextrose at 5% and sodium chloride at 0,45%	"
Dextrose at 5% and sodium chloride at 0,9%	"
Dextrose at 10%	"
Isolyte® M with dextrose at 5%	"
Ringer lactate	"
Dextrose at 5% in Ringer lactate	"
Osmitrol® at 20% in water	"
Sodium chloride at 0,9%	"
Sodium lactate	"
Normosol® M in D5W	"

Reconstituted solution must be used within 24 hours.
Solution containing dobutamine may develop a pink colour becoming always more intense. The colour may change due to a slight oxidation of the drug which, however, causes no significant loss of drug potency.

OVER-DOSAGE
Cases of over-dosage have been rarely reported.

SIGNS AND SYMPTOMS
Toxicity symptoms appear as anorexia, nausea and vomiting, tremors, anxiety, palpitations, cephalea, dyspnea, pains in the thorax of anginous and non-specific type. For its positive chronotropic and inotropic effects Miozac may cause hypertension, tachyarrhythmia, myocardial ischemia, ventricular fibrillation and hypotension.
In case of oral ingestion, the drug absorption by oral mucosa and gastrointestinal tract is unpredictable.

Administration of Miozac should be immediately interrupted, respiratory track should be re-stabilised and ventilation and perfusion should be sustained. Vital signs, blood gases and serous electrolytes should be accurately monitored and maintained within acceptable limits. Severe ventricular tachyarrhythmia may be successfully treated with propanol and lidocaine. Hypertension is normally

monitored by decrease of the dosage or interrupting the therapy. Induced diuresis, peritoneal dialysis, hemodialysis or a charcoal hemoperfusion have demonstrated no effect in case of Miozac over-dosage. In case of oral ingestion, the drugs absorption by gastrointestinal tract may be reduced by activated charcoal which is very often more efficient than vomiting induction or gastric lavage. Instead of gastric lavage or as a concomitant therapy, the use of activated charcoal is recommended. If charcoal is frequently administered it may accelerate elimination of some drugs previously absorbed. Prior to proceed to gastric lavage or activated charcoal administration the respiratory track integrity should be controlled.

ADVERSE EFFECTS
Heart rate increase, arterial pressure increase and ventricular ectopic activity increase are the most frequently observed adverse effects. In most subjects both increase of systolic pressure of 10-20 mmHg and heart rate of 5-15 pulsation/min have been reported. Increase of ventricular extrasystoles in the course of infusion has been observed in 5% of subjects.
These effects depend on dosage.

HYPOTENSION
Rapid pressure decrease have occasionally been reported. This can be easily managed by decreasing the dosage or interrupting the infusion.

REACTIONS ON SITE OF INFUSION
Phlebitis has been occasionally reported. Local inflammatory manifestations have been observed due to accidental subcutaneous in filtration.

INFREQUENT ADVERSE EFFECTS
Nausea, cephalea, anginous pain, unspecific thoracic pain, palpitation and dyspnea have been observed in 1-3% subjects.

LABORATORY ANALYSIS ALTERATIONS
Miozac, likewise other catecholamines, may cause a modest but rarely marked reduction of potassemia.

PROLONGED ADMINISTRATION
Infusion prolonged up to 72 hours have provoked no adverse effects different from those caused by a brief infusion.

A PATIENT OBSERVING ADVERSE EFFECT NOT REPORTED IN THIS LEAFLET IS ASKED TO REPORT IT TO HIS PHYSICIAN.

WARNING: DO NOT USE THE DRUG AFTER EXPIRY DATE INDICATED ON THE BOX.
THE EXPIRY DATE REFERS TO THE FINISHED PRODUCT PROPERLY STORED

SPECIAL WARNING
Product diluted for use must be utilised within 24 hours.

KEEP IT AT TEMPERATURE NOT EXCEEDING 25°C AND KEEP AWAY FROM LIGHT.

DATE OF LAST REVISION OF THE TEXT CARRIED OUT BY ITALIAN MEDICINES AGENCY:
July 2014