SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KARDİYOMİL 10 mg / 10 ml I.V. ampoule containing solution for injection / infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each 1 ml solution contains 1 mg of milrinone active substance.

Excipients:

Each 1 ml of solution,

Contains anhydrous dextrose (glucose) 0.047 g.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for sterile injection / infusion.

Clear, colorless to pale yellow, particulate free solution.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

KARDİYOMİL is indicated for the short-term treatment of severe congestive heart failure that does not respond to conventional maintenance therapy and for the treatment of patients with acute heart failure, including low output (out-put) conditions after cardiac surgery.

KARDİYOMİL is used in the pediatric population for the short-term treatment (up to 35 hours) of severe congestive heart failure that is unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators, and / or ACE inhibitors) and including low cardiac output (out-put) conditions after cardiac surgery. It is indicated for the short-term treatment (up to 35 hours) of acute heart failure.

4.2. Posology and method of administration

Posology / frequency and duration of administration:

For adults, KARDİYOMİL should first be given a loading dose of 50 pg / kg over a 10-minute period, followed by continuous infusion with a dose of 0.375 pg / kg / min and 0.750 pg / kg / min, according to hemodynamic and clinical response. The total dose should not exceed 1.13 mg / kg / day.

To prepare the 200 pg / ml infusion solution of KARDİYOMİL; 40 ml of diluent (400 ml diluent for each 100 ml ampoule) should be used for each 10 ml ampoule. The diluents used are: 0.45% sodium chloride, 0.9% sodium chloride or 5% dextrose.

The table below should be taken as basis while administration.

KARDİYOMİL injection dosage (µg /kg/min)	Infusion rate (ml/kg/hr)
0.375	0.11
0.400	0.12
0.500	0.15
0.600	0.18
0.700	0.21
0.750	0.22

Different concentrations of solutions should be used in accordance with the patient's fluid needs. Duration of treatment should depend on the patient's response. In patients with congestive heart failure, the normal duration is 48-72 hours, although treatment is continued for a maximum of 5 days. Treatment should not be continued for more than 12 hours in acute conditions following cardiac surgery.

Method of Administration:
For intravenous administration.

Additional information on special populations:
Renal impairment:
Dose adjustment is required.
In the data obtained from patients with severe renal insufficiency but without heart disease, it has been shown that the terminal elimination half-life of KARDİYOMİL increases significantly in the presence of renal failure. Loading dose is not effective in patients with clinically proven renal failure, but it is recommended to use KARDİYOMİL as shown in the table below:

Creatinine clearance (ml/min/1.73m^2)	KARDİYOMİL injection dosage (µg/kg/min)	The rate of the infusion being continued (ml/kg/hr)
5	0.20	0.06
10	0.23	0.07
20	0.28	0.08
30	0.33	0.10
40	0.38	0.11
50	0.43	0.13

The infusion rate should be adjusted according to the hemodynamic response.

Pediatric population:
Selected doses for infants and children in published studies:

-Intravenous loading dose: 50-75 μg / kg administered for 30-60 minutes.

-Intravenous continuous infusion: It is 0.25-0.75 μg / kg / min for a maximum period of 35 hours, depending on the hemodynamic response and the onset of possible side effects.

In clinical studies of low cardiac output syndrome after corrective surgery for congenital heart disease in infants and children less than 6 years of age, a loading dose of 75 μg / kg administered for 60 minutes followed by a low cardiac output of 0.75 μg / kg / min infusion over 35 hours was observed. syndrome reduced the risk of development. Pharmacokinetics
study results should also be taken into account. (See Section 5.2.)

Renal impairment:
Due to the lack of data, the use of milrinone is not recommended in pediatric patients with renal impairment (see section 4.4).

Patent ductus arteriosi:
If milrinone is desired to be used in preterm and term infants with patent ductus arteriosi risk or patent ductus arteriosi, it should be used by weighing the therapeutic requirement / potential risk ratio (See Section 4.4, 4.8.5.2 and 5.3).
No special dose adjustment is required for patients with renal insufficiency.

Geriatric population:
No specific dose adjustment is required.

4.3. Contraindications

- Hypersensitivity to the active ingredient or any of the excipients,
- It should not be used in severe hypovolemia situations.

4.4. Special warnings and precautions for use

The use of inotropic agents such as milrinone in the acute phase of myocardial infarction may cause an undesirable increase in myocardial oxygen consumption.
It is not recommended to use KARDİYOMİL immediately after acute myocardial infarction until the safety and efficacy of the patient is ensured.
During treatment with KARDİYOMİL; Careful monitoring of blood pressure, heart rate, clinical condition, electrocardiogram, fluid balance, electrolytes and renal function (e.g.; serum creatinine) is required.
In patients with severe obstructive aortic or pulmonary valve disease or hypertrophic subaortic stenosis, KARDİYOMİL should not be used instead of surgically relieving obstruction. In these

conditions, a drug with inotropic / vasodilator properties such as KARDİYOMİL may increase blood flow obstruction.
Supraventricular and ventricular arrhythmias have been observed in the high-risk population treated with KARDİYOMİL. In some patients, an increase in ventricular ectopia has been observed, including non-sustained ventricular tachycardia, which does not affect patient safety or treatment outcome.
Since it causes a small increase in A-V nodule communication, there is a possibility of increased ventricular responsiveness in patients without atrial flutter / fibrillation control. Therefore, before starting treatment with KARDİYOMİL, treatment with other agents or digitalization should be considered in order to prolong A-V nodule communication time and treatment should be discontinued in the event of arrhythmia.
Arrhythmia potential in heart failure itself may increase with many drugs or a combination of drugs. Patients receiving KARDİYOMİL should be closely monitored during the infusion and if arrhythmia develops, the infusion should be discontinued.
Due to its vasodilator effect, milrinone can cause hypotension, therefore patients with hypotension to be administered KARDİYOMİL should be carefully examined prior to treatment. Injection rate should be slowed or interrupted in patients with excessive drop in blood pressure.
If prior strong diuretic therapy is suspected to cause a significant reduction in cardiac filling pressure, KARDİYOMİL injection; It should be done by observing blood pressure, heart rate and clinical symptomatology.
With treatment with diuretics, an improvement in cardiac output requires reduction of the diuretic dose. In case of potassium loss associated with excessive diuretic intake, a reduction in diuretic dose is required. Potassium depletion due to excessive diuretics may predispose digitized patients to arrhythmia. Therefore, hypokaliemia should be corrected with potassium supplementation before or during administration with KARDİYOMİL.
Cases of reactions at the infusion site have been reported with milrinone injection (see Section 4.8. Undesirable effects). Consequently, the infusion site should be carefully observed to prevent possible extravasation.
The decrease in hemoglobin, including anemia, often occurs in cases of heart failure. Due to the risk of thrombocytopenia and anemia, patients with low platelet counts or low hemoglobin require careful monitoring of relevant laboratory parameters.
In controlled studies, there is no study for the periods exceeding 48 hours related to the infusion of Milrinone.

Pediatric population:
In addition to the warnings and precautions for adults, the following information should be considered:
Monitoring, heart rate and rhythm, systemic arterial blood pressure with umbilical artery catheter or peripheral catheter, central venous pressure, heart index, cardiac output, systemic vascular resistance, pulmonary artery pressure, atrial pressure should contain. Laboratory values to be monitored are platelet count, serum potassium, liver function, and kidney function. Frequency measurement and

evaluation should be based on baseline values and the responses of newborns to changes in therapy.
The literature reveals that there is a significant decrease in Milrinone clearance and clinically significant adverse effects in pediatric patients with impaired renal function. However, it is not yet clear at what specific creatinine clearance the dose should be adjusted in pediatric patients. Therefore, the use of Milrinone is not recommended in this population (see section 4.2).
Milrinone use in pediatric patients should be started if the patient is hemodynamically stable. Since milrinone can cause thrombocytopenia, caution should be exercised in newborns (premature babies, low birth weight) at risk of intraventricular hemorrhage. In clinical studies with pediatric patients, the risk of thrombocytopenia increased significantly with duration of infusion. Clinical data show that Milrinone-associated thrombocytopenia is more common in children than in adults (see section 4.8).
In clinical studies, it has been observed that Milrinone slows down the closure of ductus arteriosis in pediatric patients. Therefore, if the use of Milrinone in premature infants or term infants with patent ductus arteriosi is desired, the therapeutic requirements should be evaluated against potential risks (see Chapters 4.2, 4.8, 5.2 and 5.3).
This medicinal product contains approximately 0.047 g anhydrous dextrose (glucose) per 1 ml. Therefore, no glucose-related effects are expected.

4.5. Interactions with other medical products and other forms of interaction

Furosemide or bumetanide should not be administered to intravenous injection lines containing KARDİYOMİL, as a precipitate will form in the mixture.
Sodium bicarbonate should not be used for dilution in intravenous infusion administration. Although there is a theoretical potential interaction with calcium channel blockers, there is no evidence for a clinically significant interaction to date.
Milrinone has an appropriate inotropic effect without causing glycoside toxicity symptoms in patients with the digital level required for treatment in blood.
Other drugs should not be mixed with KARDİYOMİL injection, including drugs that have been found to be compatible.
Fluid and electrolyte changes and serum creatinine levels should be carefully monitored during treatment with milrinone. Improvement in cardiac output and thus diuresis may require a reduction in the dose of a diuretic agent. Potassium loss due to excessive diuresis may predispose to arrhythmia in digitized patients. Therefore, hypokaliemia before or during Milrinone use should be corrected with potassium supplements.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential/Contraception

For milrinone, clinical data on exposure to pregnancies are not available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy / embryonal / fetal development / parturition or postnatal development (see Section 5.3 Preclinical safety data).

Caution should be exercised when administered to pregnant women.

Pregnancy

Although it has not been proven in animal studies that the drug causes fetal damage or has other harmful effects on reproductive function, the safety of Milrinone has not yet been determined in humans during pregnancy. It should be used during pregnancy only by weighing the risk / benefit ratio.

Lactation

It is not known whether milrinone is excreted in human milk. Excretion of milrinone with milk has not been studied in animals. Whether or not to stop breastfeeding

The benefit of breastfeeding for the child and the benefit of KARDİYOMİL treatment for the nursing mother should be taken into account when deciding whether or not to stop / avoid treatment with KARDİYOMİL.

The reproductive capability/Fertility

No clinical data on pregnancy exposure are available for KARDİYOMİL.

4.7. Effects on ability to drive and use machines

There is no data that it affects the ability to drive and use machines.

4.8. Undesirable effects

The following undesirable effects may occur with treatment with KARDİYOMİL.

The frequency order is defined as follows:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Blood and lymphatic system disorders

Uncommon: Thrombocytopenia *

Unknown: Decrease in hemoglobin concentration and red blood cell count.

* In infants and children, the risk of thrombocytopenia increased significantly with the duration of the infusion. Clinical data indicate that milrinone-associated thrombocytopenia is more common in children than in adults.

Immune system disorders

Very rare: Anaphylactic shock

Metabolism and nutrition disorders

Uncommon: Hypokaliemia

Nervous system disorders
Common: Generally moderate to mild headache
Uncommon: Tremor

Cardiac diseases
Common: Ventricular ectopic activity, discontinuous or sustained ventricular tachycardia, supraventricular arrhythmias, hypotension.
Uncommon: Ventricular fibrillation, angina / chest pain.
Very rare: Torsades de pointes (TdP) (a type of polymorphous ventricular tachycardia that may self-terminate or degenerate into ventricular fibrillation).
The incidence of arrhythmia is not related to the dose or plasma levels of Milrinone. These arrhythmias are rarely life threatening. If arrhythmias are present, this is usually associated with pre-existing arrhythmias, metabolic abnormalities (e.g.; hypokaliemia), abnormal digoxin levels, and some underlying factors such as catheter insertion. Clinical data indicate that milrinone-associated arrhythmia is less common in children than in adults.

Respiratory, thoracic and mediastinal disorders
Very rare: Bronchospasm.

Hepato-biliary diseases
Uncommon: abnormal liver function tests

Skin and subcutaneous tissue disorders
Very rare: skin reactions such as rash.

General disorders and administration site conditions:
Unknown (cannot be estimated from the available data): Infusion site reaction.

Pediatric population:
Nervous System Diseases
Unknown: intraventricular hemorrhage (see Section 4.4).

Congenital, Familial and Genetic Diseases
Unknown: patent ductus arteriosi *** (see sections 4.2, 4.4 and 5.3)
*** Critical consequences of patent ductus arteriosi are related to the combination of excessive pulmonary circulation with sequential pulmonary edema and hemorrhage as described in the literature and decreased organ perfusion with sequential intraventricular hemorrhage and possible fatal necrotized enterocolitis.
Long-term safety data for the pediatric population are not yet available.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Intravenous overdose of KARDİYOMİL can cause hypotension (because it has vasodilator effect) and cardiac arrhythmia. If these occur, the administration of KARDİYOMİL should be reduced or stopped until the patient's condition stabilizes. There is no known specific antidote, but general measures should be taken for circulatory support.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Phosphodiesterase inhibitors
ATC Code: C01CE02

Mechanism of action:

Milrinone is a new drug with low chronotropic activity, effective, positive inotrope and vasodilator activity. It also increases left ventricular diastolic relaxation. Its structure and mode of action is different from digital glycosides, catecholamines or angiotensin converting enzyme inhibitors. It is a selective inhibitor of peak III phosphodiesterase isoenzyme in heart and vascular muscle. Milrinone provides the transmission and slight increase of the A-V node.

In clinical trials with milrinone injection, it has been shown to immediately improve hemodynamic indices in congestive heart failure, including cardiac output, pulmonary capillary occlusion pressure, and vascular resistance, with no clinically significant effect on heart rate or myocardial oxygen consumption.

Hemodynamic improvement during intravenous milrinone therapy is accompanied by clinical symptomatic improvement in congestive heart failure, as measured by the New York Heart Association classification.

Pediatric Population: A literature review has found clinical studies of patients with low cardiac output syndrome following cardiac surgery, septic shock or pulmonary hypertension. The administered doses are 50-75 μg / kg loading dose for 30-60 minutes followed by 35 hours. up to 0.25-0.75 Lig / kg / min continuous intravenous infusion. In these studies, an increase in cardiac output, decrease in cardiac filling pressure, small changes in heart rate and myocardial oxygen consumption and a decrease in systemic and pulmonary vascular resistance were observed with milrinone.

Studies on long-term milrinone use are not sufficient to recommend the administration of KARDİYOMİL for longer than 35 hours.

In some studies, the pediatric use of milrinone in patients with non-hyperdynamic septic shock (Barton et al., 1996; Lindsay et al., 1998), the effect of milrinone on post bypass pulmonary hypertension after the tetrology of Fallot repair (Chu et al., 2000); The combined effect of nitric

oxide and milrinone on the pulmonary circulation after phantom type procedure (Cai et al., 2008) was investigated.
The results of these studies are insufficient. Therefore, milrinone is not recommended for these indications.

5.2. Pharmacokinetic properties

General Particulars

Distribution:
Following 12.5 Lg / kg - 125 Lg / kg intravenous injection of KARDİYOMİL to patients with congestive heart failure; distribution is 0.38 liters / kg / hour, mean terminal elimination half-life 2.3 hours and clearance 0.13 liters / kg / hour.
Following 0.20 - 0.70 Lg / kg / minute intravenous infusion to patients with congestive heart failure; volume of distribution: 0.45 liters / kg, mean terminal elimination half-life: 2.4 hours and clearance 0.14 liters / kg / hour.
These pharmacokinetic parameters are not dose dependent, and the area under the plasma concentration versus time curve following injections is significantly dose dependent.
KARDİYOMİL has been shown to bind approximately 70% (by equilibrium dialysis) to human plasma protein.

Biotransformation:
It has 5 metabolites but the O-glucuronide metabolite represents the major part of biotransformation.

Elimination:
The main excretion of orally administered milrinone occurs through the urinary tract (83%) and its metabolite O-glucuronide (12%).
In normal individuals, elimination is rapid through the urinary tract, after administration of the drug, the recovery is approximately 60% within the first two hours and the recovery is approximately 90% within the first eight hours. The average renal clearance of milrinone is approximately 0.3 liter / min, which is indicative of active outbreak.

Linearity / Nonlinear case:
No information available.

Pediatric Population
Milrinone clears up faster in children than adults. However, the clearance of infants is significantly lower than that of children. Clearance is lower in preterm babies. Steady-state plasma concentrations of milrinone are lower in children than adults, due to the faster clearance than adults. In the pediatric population with normal renal functions, steady state milrinone plasma concentration is approximately 100-300 ng / ml after 6-12 hours of continuous infusion of 0.5-0.75 µg / kg / min.
After open heart surgery, the distribution volume of milrinone after 0.5-0.75 µg / kg / min intravenous infusion in newborns, infants and children is between 0.35-0.9 L / kg without any

significant change between age groups. The distribution volume of milrinone is approximately 0.5 liter / kg following 0.5 μg / kg / min intravenous infusion administered to very preterm babies to prevent low system output after birth.
Many pharmacokinetic studies have shown that clearance increases with increasing age in the pediatric population. Infants have significantly lower clearance (3.4-3.8 ml / kg / min) than children (5.9-6.7 ml / kg / min). Milrinone clearance in newborns is approximately 1.64 ml / kg / min; In preterm infants, the clearance is lower (0.64 ml / kg / min).
The mean terminal elimination half-life of milrinone is 2-4 hours in infants and children and 10 hours in preterm infants.
It is concluded that in pediatric patients, the optimum dose of milrinone is higher than in adults to achieve a value above the threshold of pharmacodynamic activity;
however, in preterm infants, the optimum dose required to achieve a value above the threshold of pharmacodynamic efficiency is lower than in children.
Patent ductus arteriosi: Milrinone is excreted through the kidney and has a volume of distribution limited by the extracellular space. This indicates that the excess fluid and hemodynamic changes associated with patent ductus arteriosi have an effect on the distribution and excretion of Milrinone.

5.3. Preclinical safety data

Juvenile Animals: A preclinical study was conducted to explain the ductus-expanding effects of PDE 3 inhibitors in recent rat pups and their differential effects in near term preterm fetal rats. Postnatal ductus dilation with milrinone was studied at 3 doses (10.1 and 0.1 mg / kg). The dilator effect was studied by the simultaneous administration of milrinone (10.1 and 0.1 mg / kg) and indomethacin (10 mg / kg) to the mother rat D21 (near term) and D19 (preterm) to the fetal duct contracted by indomethacin. It has been shown that the dilatation effects of the injection applied immediately after birth are more potent than the one hour after birth. Also, this study showed that immature ductus arteriosi is more sensitive to milrinone than mature ductus arteriosi. (See Sections 4.2,4.4,4.8 and 5.2).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactic acid
Anhydrous dextrose (glucose), Sodium hydroxide, Water for injection

6.2. Incompatibilities

Furosemide or bumetanide should not be administered to intravenous injection lines containing KARDİYOMİL, as a precipitate will form in the mixture. Sodium bicarbonate should not be used for dilution in intravenous infusion administration.
Other drugs should not be mixed with KARDİYOMİL injection.

6.3. Shelf life

24 months

Infusion solutions; It should be used within 24 hours by diluting with the recommended 0.45% sodium chloride, 0.9% sodium chloride or 5% dextrose.

6.4. Special precautions for storage

It should be stored at room temperature below 25 ° C, do not freeze.

6.5. Nature and contents of container

10 ml solution in colorless Type I glass ampoules - 1 ampoule / box..

6.6. Special precautions for disposal and other handling

The drug should be visually inspected, containing particulate matter or has been colored solutions should not be used.

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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