**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1 NAME OF THE MEDICINAL PRODUCT

# Primacor Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 1mg/ml of the active substance Milrinone

For a full list of excipients see section 6.1

## 3 PHARMACEUTICAL FORM

Solution for Injection.

Clear, colourless to pale yellow liquid.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Primacor injection is indicated for treatment of refractory heart failure immediately (up to 72 hours) following cardiac surgery.
For the short-term (up to 48 hours) intravenous therapy of severe refractory congestive heart failure.

In pediatric population Primacor is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of pediatric patients with acute heart failure, including low output states following cardiac surgery.

### 4.2 Posology and method of administration

For intravenous administration

*Adults*:
Primacor Injection should be given as a loading dose of 50µg/kg administered over a period of 10 minutes usually followed by a continuous infusion at a dosage titrated between 0.375 µg/kg/min and 0.75 µg /kg/min according to haemodynamic and clinical response, but should not exceed 1.13mg/kg/day total dose.

The following provides a guide to maintenance infusion delivery rate based upon a solution containing milrinone 200 µg /ml prepared by adding 40ml diluent per 10ml ampoule (400ml diluent per 100ml Primacor Injection). 0.45% saline, 0.9% saline or 5% dextrose may be used as diluents.

| **Primacor Injection Dose (µg /kg/min)** | **Infusion Delivery Rate (ml/kg/h)** |
|---|---|
| 0.375 | 0.11 |
| 0.400 | 0.12 |
| 0.500 | 0.15 |
| 0.600 | 0.18 |
| 0.700 | 0.21 |
| 0.750 | 0.22 |

Solutions of different concentrations may be used according to patient fluid requirements. The duration of therapy should depend upon the patient's response. In congestive cardiac failure, patients have been maintained on the infusion for up to 5 days, although the usual period is 48 to 72 hours. In acute states following cardiac surgery, it is unlikely that treatment need be maintained for more than 12 hours.

*Renal Impairment:*
Dosage adjustment required (see section 4.4).
Data obtained from patients with severe renal impairment but without heart failure have demonstrated that the presence of renal impairment significantly increases the terminal elimination half-life of milrinone. For patients with clinical evidence of renal impairment, the loading dose is not affected, but the following maintenance infusion rates are recommended using the infusion solution described above.

| Creatinine Clearance (ml/min/1.73m$^2$) | Primacor Injection Dose (µg /kg/min) | Maintenance Infusion Delivery Rate (ml/kg/h) |
|---|---|---|
| 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 haemodynamic response.

*Elderly*: Experience so far suggests that no special dosage recommendations are necessary.

*Pediatric population:*
In published studies selected doses for infants and children were:
• Intravenous loading dose: 50 to 75 µg/kg administered over 30 to 60 minutes.
• Intravenous continuous infusion: To be initiated on the basis of hemodynamic response and the possible onset of undesirable effects between 0.25 to 0.75 µg/kg/min for a period up to 35 hours.

In clinical studies on low cardiac output syndrome in infants and children under 6 years of age after corrective surgery for congenital heart disease 75 µg/kg loading dose over 60 minutes followed by a 0.75 µg/kg/min infusion for 35 hours significantly reduced the risk of development of low cardiac output syndrome.

Results of pharmacokinetic studies (see section 5.2) have to be taken into consideration.

*Renal impairment in pediatric population:*
Due to lack of data the use of milrinone is not recommended in pediatric population with renal impairment (for further information please *see section 4.4*).

*Patent ductus arteriosus:*
If the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.4, 4.8, 5.2, and 5.3).

## 4.3 Contraindications

- Hypersensitivity to milrinone.or any of the excipients.
- Severe hypovolaemia

## 4.4 Special warnings and special precautions for use

The use of inotropic agents such as milrinone during the acute phase of a myocardial infarction may lead to an undesirable increase in myocardial oxygen consumption ($MVO_2$). Primacor Injection is not recommended immediately following acute myocardial infarction until safety and efficacy have been established in this situation.

Careful monitoring should be maintained during Primacor Injection therapy including blood pressure, heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function (i.e. serum creatinine).

In patients with severe obstructive aortic or pulmonary valvular disease or hypertrophic subaortic stenosis, Primacor Injection should not be used in place of surgical relief of the obstruction. In these conditions it is possible that a drug with inotropic / vasodilator properties might aggravate outflow obstruction.

Supraventricular and ventricular arrhythmias have been observed in the high risk population treated with milrinone. In some patients an increase in ventricular ectopy including non-sustained ventricular tachycardia has been observed which did not affect patient safety or outcome.
The potential for arrhythmia, present in heart failure itself, may be increased by many drugs or a combination of drugs. Patients receiving Primacor Injection should be closely monitored during infusion and the infusion should be stopped if arrhythmias develop.

As milrinone produces a slight enhancement in A-V node conduction, there is a possibility of an increased ventricular response rate in patients with uncontrolled atrial flutter / fibrillation. Consideration should therefore be given to digitalisation or treatment with other agents to prolong A-V node conduction time prior to starting Primacor Injection therapy, and to discontinuing the therapy if arrhythmias occur.

Milrinone may induce hypotension as a consequence of its vasodilatory activity, therefore caution should be exercised when Primacor Injection is administered to patients who are hypotensive prior to treatment. The rate of infusion should be slowed or stopped in patients showing excessive decreases in blood pressure.

If prior vigorous diuretic therapy is suspected of having caused significant decreases in cardiac filling pressure, Primacor Injection should be cautiously administered while monitoring blood pressure, heart rate and clinical symptomatology.

Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalised patients to arrhythmias. Therefore, hypokalaemia should be corrected by potassium supplementation in advance of, or during, the use of Primacor Injection.

Decrease in haemoglobin, including anaemia, often takes place in the setting of cardiac failure. Due to the risk of thrombocytopenia or anaemia, careful monitoring of the corresponding laboratory parameters is required in patients with decreased platelet count or decreased haemoglobin.

There is no experience in controlled trials with infusions of milrinone for periods exceeding 48 hours.

Cases of infusion site reaction have been reported with Primacor injection (see section 4.8 Undesirable effects). Consequently, careful monitoring of the infusion site should be maintained so as to avoid possible extravasation.

***Use in the elderly***:
There are no special recommendations for elderly patients. No age-related effects on the incidence of adverse reactions have been observed. Controlled pharmacokinetic studies have not shown changes in the pharmacokinetic profile of milrinone in the elderly.

***Renal impairment***:
In patients with severe renal impairment dosage adjustment is required (*see section 4.2 Posology and method of administration*).

***Pediatric population***:
The following should be considered in addition to the warnings and precautions described for adults:

In neonates, following open- heart surgery during Primacor therapy, monitoring should include heart rate and rhythm, systemic arterial blood pressure via umbilical artery catheter or

peripheral catheter, central venous pressure, cardiac index, cardiac output, systemic vascular resistance, pulmonary artery pressure, and atrial pressure. Laboratory values that should be followed are platelet count, serum potassium, liver function, and renal function. Frequency of assessment is determined by baseline values, and it is necessary to evaluate the neonate's response to changes in therapy.

Literature revealed that in pediatric patients with impaired renal function, there were marked impairment of milrinone clearance and clinically significant side effects, but the specific creatinine clearance at which doses must be adjusted in pediatric patients is still not clear, therefore the use of milrinone is not recommended in this population (see section 4.2).

In pediatric patients milrinone should be initiated only if the patient is hemodynamically stable.

Caution should be exercised in neonates with risk factors of intraventricular haemorrhage (i.e. preterm infant, low birth weight) since milrinone may induce thrombocytopenia. In clinical studies in pediatric patients, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (*see section 4.8*).

In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in pediatric population. Therefore, if the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (*see sections 4.2, 4.8, 5.2 and 5.3*).

## 4.5 Interaction with other medicinal products and other forms of interactions

Furosemide or bumetanide should not be administered in intravenous lines containing milrinone lactate in order to avoid precipitation.

Milrinone should not be diluted in sodium bicarbonate intravenous infusion.

Whilst there is a theoretical potential interaction with calcium channel blockers, there has been no evidence of a clinically significant interaction to date.

Milrinone has a favourable inotropic effect in fully digitalised patients without causing signs of glycoside toxicity.

Fluid and electrolyte changes, as well as serum creatinine levels, should be carefully monitored during treatment with milrinone. Improvement in cardiac output and consequently, diuresis, may require reduction in the dose of a diuretic agent. Potassium loss due to excessive diuresis may predispose digitalised patients to arrhythmias. Therefore, hypokalaemia should be corrected by potassium supplementation in advance of, or during milrinone use.

## 4.6 Pregnancy and lactation

***Use in Pregnancy***

Although animal studies have not revealed evidence of drug-induced foetal damage or other deleterious effects on reproductive function, the safety of milrinone in human pregnancy has not yet been established. It should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

***Use in Lactation***

There is insufficient information on the excretion of milrinone in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue milrinone therapy taking into account the benefit of breast feeding for a child and the benefit of therapy for the woman.

## 4.7 Effects on ability to drive and to use machines

No studies on the effect on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Adverse reactions have been ranked under heading of system-organ class and frequency using the following convention: very common (≥1/10); common (≥1/100, ≤1/10); uncommon (≥1/1,000, ≤1/100); rare (≥ 1/10,000, ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders**:

- Uncommon: Thrombocytopenia*
- Not known: reduction of red blood count and/or haemoglobin concentration

*In infants and children, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.4).

**Immune system disorders**:

- Very rare: Anaphylactic shock

**Metabolism and nutrition disorders:**

- Uncommon: Hypokalaemia

**Nervous System disorders:**

- Common: Headaches, usually mild to moderate in severity
- Uncommon: Tremor

**Cardiac disorders:**

- Common:
  - Ventricular ectopic activity
  - Non sustained or sustained ventricular tachycardia (see section 4.4)
  - Supraventricular arrhythmias
  - Hypotension
- Uncommon:
  - Ventricular fibrillation
  - Angina/chest pain
- Very rare:
  - Torsades de pointes

The incidence of arrhythmias has not been related to dose or plasma levels of milrinone. These arrhythmias are rarely life- threatening. If present, they are often associated with certain underlying factors such as pre-existing arrhythmias, metabolic abnormalities (e.g. hypokalaemia), abnormal digoxin levels and catheter insertion. Clinical data suggest that milrinone-related arrhythmias are less common in children than in adults.

**Respiratory, thoracic and mediastinal disorders**:

- Very rare: Bronchospasm

**Hepato-biliary disorders**:

- Uncommon: liver function tests abnormality

**Skin and subcutaneous tissue disorders**:

- Very rarely: skin reactions such as rash

**Renal and urinary disorders**

- Not known: Renal failure, secondary to a concomitant hypotension

**General disorders and administration site reactions**

- Not known: Infusion site reaction

**Pediatric population**:

Nervous system disorders
Not known: intraventricular haemorrhage (see section 4.4)

Congenital, familial, and genetic disorders
Not known: patent ductus arteriosus*** (see sections 4.2, 4.4, 5.2 and 5.3)

***The critical consequences of the patent ductus arteriosus are related to a combination of pulmonary overcirculation with consecutive pulmonary oedema and haemorrhage and of reduced organ perfusion with consecutive intraventricular haemorrhage and necrotizing enterocolitis with possible fatal outcome as described in literature.

Long-term safety data for pediatric population are not yet available.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il).

## 4.9 Overdose

Overdose of intravenous Primacor may produce hypotension (because of its vasodilatory effect) and cardiac arrhythmia. If this occurs, Primacor Injection administration should be reduced or temporarily discontinued until the patient's condition stabilises. No specific antidote is known, but general measures for circulatory support should be taken.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy; Phosphodiesterase inhibitor, ATC code C01CE02

Milrinone is a positive inotrope and vasodilator, with little chronotropic activity. It also improves left ventricular diastolic relaxation. It differs in structure and mode of action from the digitalis glycosides, catecholamines or angiotensin-converting enzyme inhibitors. It is a selective inhibitor of peak III phosphodiesterase isoenzyme in cardiac and vascular muscle. It produces slight enhancement of A-V node conduction, but no other significant electro-physiological effects.

In clinical studies Primacor Injection has been shown to produce prompt improvements in the haemodynamic indices of congestive heart failure, including cardiac output, pulmonary capillary wedge pressure and vascular resistance, without clinically significant effect on heart rate or myocardial oxygen consumption. Haemodynamic improvement during intravenous Primacor therapy is accompanied by clinical symptomatic improvement in congestive cardiac failure, as measured by change in New York Heart Association classification.

Pediatric population:
Literature review identified clinical studies with patients treated for low cardiac output syndrome following cardiac surgery, septic shock or pulmonary hypertension. The usual dosages were a loading dose of 50 to 75 µg/kg administered over 30 to 60 minutes followed by an intravenous continuous infusion of 0.25 to 0.75 µg/kg/min for a period up to 35 hours. In these studies, milrinone demonstrated an increase of cardiac output, a decrease in cardiac filling pressure, a decrease in systemic and pulmonary vascular resistance, with minimal changes in heart rate and in myocardial oxygen consumption.

Studies of a longer use of milrinone are not sufficient to recommend an administration of milrinone during a period of more than 35 hours.

Some studies explored 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 postbypass pulmonary hypertension after tetralogy of Fallot repair (Chu et al., 2000); the combined effect

of nitric oxide and milrinone on pulmonary circulation after Fontan-type procedure (Cai et al., 2008).

The results of these studies were inconclusive. Therefore, the use of milrinone in these indications cannot be recommended.

## 5.2 Pharmacokinetic properties

Following intravenous injections of 12.5 to 125 µg/kg to congestive heart failure patients, Primacor Injection had a volume of distribution of 0.38 l/kg/h, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 l/kg/h. Following intravenous infusions of 0.2 to 0.7 µg/kg/min to congestive heart failure patients, the drug had a volume of distribution of about 0.45 l/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14 l/kg/h. These pharmacokinetic parameters were not dose-dependent, and the area under the plasma concentration versus time curve following injection was significantly dose-dependent.

The primary route of excretion of milrinone in man is via the urine. Elimination in normal subjects via the urine is rapid, with approximately 60% recovered within the first two hours following dosing, and approximately 90% recovered within the first eight hours following dosing. The mean renal clearance of milrinone is approximately 0.3 l/min, indicative of active secretion.

**Pediatric population**:

Milrinone is cleared more rapidly in children than in adults, but infants have significantly lower clearance than children, and preterm infants have even lower clearance. As a consequence of this more rapid clearance compared to adults, steady-state plasma concentrations of milrinone were lower in children than in adults. In pediatric population with normal renal function steady-state milrinone plasma concentrations after 6 to 12 hours continuous infusion of 0.5 to 0.75 µg/kg/min were about of 100 to 300 ng/ml.

Following intravenous infusion of 0.5 to 0.75 µg/kg/min to neonates, infants and children after open-heart surgery, milrinone has a volume of distribution ranging from 0.35 to 0.9 litres/kg with no significant difference across age groups. Following intravenous infusion of 0.5 µg/kg/min to very preterm infants to prevent low systemic outflow after birth, milrinone has a volume of distribution of about 0.5 litres/kg.

Several pharmacokinetic studies showed that, in pediatric population, clearance increases with increasing age. Infants have significantly lower clearance than children (3.4 to 3.8 ml/kg/min versus 5.9 to 6.7 ml/kg/min). In neonates milrinone clearance was about 1.64 ml/kg/min and preterm infants have even lower clearance (0.64 ml/kg/min).
Milrinone has a mean terminal half-life of 2 to 4 hours in infants and children and a mean terminal elimination half-life of 10 hours in preterm infants.

It was concluded that the optimal dose of milrinone in pediatric patients in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared higher than in adults, but that optimal dose in preterms in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared lower than in children.

Patent ductus arteriosus:
Milrinone is cleared by renal excretion and has a volume of distribution that is restricted to extracellular space which suggests that the fluid overload and hemodynamic changes associated with patent ductus arteriosus may have an effect on distribution and excretion of milrinone (see sections 4.2, 4.4, 4.8 and 5.3).

## 5.3 Preclinical safety data

Juvenile animals:
A preclinical study was performed to clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm foetal rats. Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10, 1 and 0.1mg/kg). The dilating effects of milrinone in the foetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone (10, 1 and 0.1mg/kg) and indomethacin (10 mg/kg) to the mother rat at D21 (near-term) and D19 (preterm). This in vivo study has shown that milrinone induces dose-dependent dilation of the foetal and the postnatal constricted ductus

arteriosus. Dilating effects were more potent with injection immediately after birth than at 1 hour after birth. In addition, study showed that the premature ductus arteriosus is more sensitive to milrinone than the mature ductus arteriosus (see sections 4.2, 4.4, 4.8 and 5.2).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Lactic Acid, Dextrose Anhydrous, Water for Injection, Sodium Hydroxide.

### 6.2 Incompatibilities

Furosemide or bumetanide should not be administered in intravenous lines containing Primacor Injection since precipitation occurs on admixture. Sodium Bicarbonate Intravenous infusion should not be used for dilution.

Other drugs should not be mixed with Primacor Injection until further compatibility data are available.

### 6.3 Shelf life

36 months when unopened.
A diluted solution of Primacor Injection should be used within 24 hours.

### 6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

### 6.5 Nature and contents of container

Type 1 clear glass ampoules 10ml packed in lots of 10.

### 6.6 Special precautions for disposal

Infusion solutions diluted as recommended with 0.45% saline, 0.9% saline or 5% dextrose should be freshly prepared before use. Parenteral drug products should be examined visually and should not be used if particulate matter or discolouration are present.

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