For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated; please read carefully using a new pack.

Milrinone Lactate Injection
Primacor®

DESCRIPTION

Active Moiety / Active Ingredient
Milrinone Lactate

Therapeutic or Pharmacological Class
Selective inhibitor of phosphodiesterase isoenzyme type III

Pharmaceutical Form
Solution for intravenous injection / infusion at 1mg/ml milrinone.
Clear, colourless to pale yellow liquid

Composition
Each ml of solution contains: 1mg of milrinone as the lactate salt
Excipients: dextrose anhydrous, water for injection, lactic acid or sodium hydroxide qs for pH range of 3.2 to 4.0

INDICATIONS
Primacor® is indicated for the short-term intravenous therapy of severe congestive heart failure irresponsive to conventional maintenance therapy and in acute heart failure including low output states following cardiac surgery.

DOSAGE AND ADMINISTRATION

General
For intravenous administration.
Primacor® therapy should be initiated with a loading dose, usually followed by a continuous infusion (maintenance dose) according to the following guideline:

DOSAGE

Adults

- Loading dose : 50 micrograms/kg; administered slowly (over a period of 10 minutes)
- Maintenance dose 0.375 to 0.75 micrograms/kg/min. The infusion rate should be adapted to hemodynamic and clinical response, but should not exceed the maximum daily dose of 1.13 mg/kg. Solutions of various concentrations may be used, depending on the patient's fluid requirements.

Children

- 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.

Elderly: Experience to date would tend to suggest that, assuming normal renal function, no special dosage recommendations are necessary for this age group.

Renal impairment:
Dosage adjustment required. See Precautions.
Dosage adjustment in patients with renal impairment is based on data obtained from patients with severe renal impairment but without congestive heart failure, who show significant increases to the terminal elimination half-life of milrinone. The loading dose is not affected, but a reduction in the maintenance infusion rate may be necessary depending on the severity (creatinine clearance) of the renal impairment (see table below)

Creatinine Clearance ($ml/min/1.73m^2$)	Infusion Rate (µg/kg/min)
5	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

Due to lack of data the use of milrinone is not recommended in paediatric patients with renal impairment (see Section Precautions).

Administration-
The table below shows the loading dose in milliliters (mL) of milrinone (1mg/mL) versus patient body weight (kg).

LOADING DOSE (mL)
(using 1 mg/mL concentration)

Patient Body Weight (kg) vs loading volume milrinone (mL)										
kg	30	40	50	60	70	80	90	100	110	120
mL	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0

The loading dose may be given undiluted, but diluting to a rounded total volume of 10 or 20 mL may simplify the visualization of the injection rate (10 minute period).

MAINTENANCE DOSE
(continuous intravenous infusion)

	Infusion rate	Total Daily dose (24 Hours)
Minimum	0.375 mcg/kg/min	0.59mg/kg
Standard	0.50mcg/kg/min	0.77 mg/kg
Maximum	0.75mcg/kg/min	1.13mg/kg

Suitable diluents include 0.45% Sodium Chloride, 0.9% Sodium Chloride, or sterile 5% dextrose solution.
Primacor® should not be diluted in sodium bicarbonate. Diluted solution should be used within 24 hours.

CONTRAINDICATIONS

Hypersensitivity to milrinone or excipients**.**

WARNINGS

In patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis, Primacor® should not be used in lieu of surgical relief of the obstruction. As with other drugs with inotropic/ vasodilator properties, Primacor® may aggravate outflow obstruction in these conditions. No clinical studies have been conducted in patients in the acute phase of post myocardial infarction. Use of Primacor® in such a context is not recommended as this may lead to an undesirable increase in myocardial oxygen consumption (MVO_2). Primacor® has not been shown to increase myocardial oxygen consumption in patients with chronic heart failure. In pediatric clinical studies, exposure to milrinone, appeared to slow the closure of the ductus arteriosus. Therefore the therapeutic need must be weighed against potential risks (see Adverse Reactions).

PRECAUTIONS

Primacor® may induce hypotension as a consequence of its vasodilatory action. Caution should therefore be exercised in patients with hypotension prior to treatment, or those showing excessive decreases in blood pressure during treatment with Primacor®. In such cases, the infusion should be discontinued until the hypotensive effect has been resolved, and then resumed, if necessary, at a lower rate of infusion. If prior vigorous diuretic therapy is suspected to have caused significant decreases in cardiac filling pressure, Primacor® should be administered with caution while monitoring blood pressure, heart rate, and other clinically relevant symptoms.

Fluid and electrolyte changes, as well as serum creatinine levels should be carefully monitored during treatment with Primacor®. 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, hypokaliemia should be corrected by potassium supplementation in advance of, or during Primacor® use.
As the potential for arrhythmia, already prevalent in heart failure, may be increased by many drugs or combination of drugs, patients receiving Primacor® should be closely monitored during infusion (heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function (i.e. serum creatinine).

Supraventricular and ventricular arrhythmias have been observed in the high-risk population requiring treatment with Primacor®. In some patients, an increase in ventricular ectopy including non-sustained ventricular tachycardia has been observed.

As Primacor® 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. In these patients, prior digitalisation or treatment with other agents to prolong atrio-ventricular node conduction time should be considered.

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 intravenous milrinone therapy (see Adverse Reactions). Consequently, careful monitoring of the infusion site should be maintained so as to avoid possible extravasation

Elderly: There are no special recommendations for elderly patients.
Controlled pharmacokinetic studies have not disclosed any age-related effects on the distribution and elimination of Primacor®.

Renal impairment: Dosage adjustment required in adult patients (See Special Populations). According to literature data, milrinone clearance may be significantly impaired in paediatric patients with impaired renal function and clinically significant side effects may be increased. Therefore the use of milrinone is not recommended in this population (see Special Populations).

INTERACTIONS

When furosemide is injected into an intravenous line delivering milrinone lactate, a precipitate is formed. Therefore, furosemide or bumetanide should not be administered in intravenous lines containing milrinone lactate.

Milrinone lactate should not be diluted in sodium bicarbonate intravenous infusion.
Other drugs should not be mixed with Primacor® until further compatibility data are available.

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.

LACTATION

No information is available to indicate whether milrinone is excreted in breast milk.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Not applicable.

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10 %) ; Common (≥ 1 % and < 10%); Uncommon (≥ 0.1 % and < 1%) ;
Rare (≥ 0.01 % and < 0.1%); Very rare (< 0.01%), *Unknown (cannot be estimated from available data).*

Blood and the lymphatic system disorders:

Uncommon: Thrombocytopenia
In infants and children, the longer the duration of infusion, the higher is the risk of thrombocytopenia. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults.

Metabolism and nutrition disorders:
Uncommon: Hypokalemia

Nervous system disorders:
Common: Headaches

Uncommon: Tremor

Cardiac disorders:
Common: Ventricular ectopic activity, ventricular tachycardia (non sustained or sustained), supra-ventricular arrhythmias, hypotension**.**
Uncommon: Ventricular fibrillation, angina/chest pain.
Very rare: Torsade de pointes**.**

No relationship has been established between the incidence of supraventricular or ventricular arrhythmias, and the plasma level of milrinone. Life threatening arrhythmias are often found to be associated with underlying risk factors such as pre-existing arrhythmias, metabolic anomalies (e.g. hypokalemia), elevated serum digoxin levels or 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 abnormal.

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

Renal and urinary disorders
Not known: Renal failure, secondary to a concomitant hypotension

General disorders and administration site conditions
Not Known: Infusion site reaction.
Very rare: Anaphylactic shock.

Congenital, familial, and genetic disorders
Not known: patent ductus arteriosus (see Precautions)

OVERDOSE
Signs and Symptoms: High doses of milrinone lactate may induce hypotension and cardiac arrhythmia.

Management: Administration of milrinone lactate should be discontinued until the patient's condition stabilises. No specific antidote for milrinone is known; general measures of circulatory support should be taken.

ABUSE AND DEPENDENCE

Not applicable

INCOMPATIBILITIES / COMPATIBILITIES

When furosemide is injected into an intravenous line delivering milrinone lactate a precipitate is formed. Therefore, furosemide or bumetanide should not be administered in intravenous lines containing milrinone lactate. Primacor® should not be diluted in sodium bicarbonate for intravenous infusion.

STORAGE CONDITIONS AND SHELF-LIFE

Store below 25°C. Do not freeze.
Shelf life: See outer carton.
A diluted solution of Primacor® should be used within 24 hours.

PREPARATION AND HANDLING

Intravenous drug products should be inspected visually and should not be used if particulate matter or discolouration is present.

Suitable diluents include normal (0.9%) or half normal (0.45%) saline, or sterile 5% dextrose solution. Primacor® should not be diluted in sodium bicarbonate. Diluted solution should be used within 24 hours.

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