Milrinone Lunan 1 mg/ml Solution for Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1mg/ml of the active substance Milrinone.
Each ml contain: Milrinone lactate 1.4265mg (equivalent to milrinone 1mg).

For excipients, see List of Excipients

PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow liquid.

CLINICAL PARTICULARS

Therapeutic indications

Milrinone Lactate Injection is indicated for the short-term intravenous treatment of patients with acute decompensated heart failure. Patients receiving Milrinone Lactate Injection should be observed closely with appropriate electrocardiographic equipment. The facility for immediate treatment of potential cardiac events, which may include life threatening ventricular arrythmias, must be available. The majority of experience with intravenous Milrinone Lactate Injection has been in patients receiving digoxin and diuretics.
There is no experience in controlled trials with infusions of Milrinone Lactate Injection for periods exceeding 48 hours.

Posology and method of administration

Milrinone Lactate Injection should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:
LOADING DOSE
50 mcg/kg: Administer slowly over 10 minutes
The table below shows the loading dose in milliliters (mL) of Milrinone Lactate Injection (1mg/mL) by patient body weight (kg).
Loading Dose (mL) Using 1 mg/mL Concentration

Patient Body Weight (kg)										
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 (see Maintenance Dose for diluents) may simplify the visualization of the injection rate.

MAINTENANCE DOSE

	Infusion Rate	Total Daily Dose	

		(24 Hours)	
Minimum Standard Maximum	0.375 mcg/kg/min 0.50 mcg/kg/min 0.75 mcg/kg/min	0.59 mg/kg 0.77 mg/kg 1.13 mg/kg	Administer as a continuous intravenous infusion

Milrinone Lactate drawn from vials should be diluted prior to maintenance dose administration. The diluents that may be used are 0.45% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose Injection USP. The table below shows the volume of diluent in milliliters (mL) that must be used to achieve 200 mcg/mL concentration for infusion, and the resultant total volumes.

Desired Infusion Concentration mcg/mL	Milrinone Lactate Injection 1 mg/mL (mL)	Diluent (mL)	Total Volume (mL)
200	10	40	50
200	20	80	100

The infusion rate should be adjusted according to hemodynamic and clinical response. Patients should be closely monitored. In controlled clinical studies, most patients showed an improvement in hemodynamic status as evidenced by increases in cardiac output and reductions in pulmonary capillary wedge pressure.
Note: See "**Dosage Adjustment in Renally Impaired Patients.**" Dosage may be titrated to the maximum hemodynamic effect and should not exceed 1.13 mg/kg/day.
Duration of therapy should depend upon patient responsiveness.
The maintenance dose in mL/hr by patient body weight (kg) may be determined by reference to the following table.

Milrinone Infusion Rate (mL/hr) Using 200 mcg/mL Concentration

Maintenance Dose (mcg/kg/min)	Patient Body Weight (kg)									
	30	40	50	60	70	80	90	100	110	120
0.375	3.4	4.5	5.6	6.8	7.9	9.0	10.1	11.3	12.4	13.5
0.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0	13.2	14.4
0.5	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0
0.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0	19.8	21.6
0.7	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21.0	23.1	25.2
0.75	6.8	9.0	11.3	13.5	15.8	18.0	20.3	22.5	24.8	27.0

When administering milrinone lactate by continuous infusion, it is advisable to use a calibrated electronic infusion device.
Intravenous drug products should be inspected visually and should not be used if particulate matter or discoloration is present.

Dosage Adjustment in Renally Impaired Patients
Data obtained from patients with severe renal impairment (creatinine clearance = 0 to 30 mL/min) but without congestive heart failure have demonstrated that the presence of renal

impairment significantly increases the terminal elimination half-life of Milrinone Lactate Injection. Reductions in infusion rate may be necessary in patients with renal impairment. For patients with clinical evidence of renal impairment, the recommended infusion rate can be obtained from the following table:

Creatinine Clearance (mL/min/1.73m^2)	Infusion Rate (mcg/kg/min)
5	0.2
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

Contraindications

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

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 (MVO2).

Milrinone Lactate 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 Milrinone Lactate 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, Milrinone Lactate 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 Milrinone Lactate 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 Milrinone Lactate 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 Milrinone Lactate 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 Milrinone Lactate 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 Milrinone Lactate 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 Milrinone Lactate Injection. 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.

In patients with severe renal impairment dosage adjustment is required

Interaction with other medicinal products and other forms of interaction
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.

Fertility, 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.

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

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

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
  - 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 abnormal

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

General disorders and administration site conditions:
- Not known: Infusion site reaction

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

Overdose
Overdose of intravenous Milrinone Lactate Injection may produce hypotension (because of its vasodilatory effect) and cardiac arrhythmia. If this occurs, Milrinone Lactate 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.

PHARMACOLOGICAL PROPERTIES
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 Milrinone Lactate 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 Milrinone Lactate Injection therapy is accompanied by clinical symptomatic improvement in congestive cardiac failure, as measured by change in New York Heart Association classification.

Pharmacokinetic properties
Following intravenous injections of 12.5 to 125mcg/kg to congestive heart failure patients, Milrinone Lactate Injection had a volume of distribution of 0.38 l/kg/hr, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 l/kg/hr. Following intravenous infusions of 0.2 to 0.7mcg/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/hr. 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.

PHARMACEUTICAL PARTICULARS

List of excipients
Lactic Acid, Dextrose Anhydrous, Water for Injection, Sodium Hydroxide (for pH adjustment)

Incompatibilities
Furosemide or bumetanide should not be administered in intravenous lines containing Milrinone Lactate Injection since precipitation occurs on admixture. Sodium Bicarbonate Intravenous infusion should not be used for dilution.
Other drugs should not be mixed with Milrinone Lactate Injection until further compatibility data are available.

Storage Conditions:
Unopened vial: Do not store above 30°C.

A diluted solution of Milrinone Lactate Injection should be used within 24 hours. Store at room temperature (25°C) after dilution.

Shelf life
As indicated on the outer box.

Nature and contents of container
Pack size: 10mL x 10 vials

10mL vial: Neutral borosilicate glass tubular injection vials

Stopper: elastomer formulations, coatings, aluminum seals-bromobutyl rubber stoppers

Aluminum flip-off seal: Aluminum plastic combination cover

Special precautions for disposal
Infusion solutions diluted as recommended with 0.45% Sodium Chloride Inj USP, 0.9% Sodium Chloride Inj USP or 5% Dextrose Inj USP 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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