Milrinone Lactate Injection USP 10mg/10mL (1mg/mL)

MilriNext
मिलरीनेक्स्ट

For use in India only

To be sold by retail on the prescription of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

1. GENERIC NAME
Milrinone Lactate Injection USP 10mg/10mL (1mg/mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Milrinone Lactate Injection USP 10mg/10 ml (1mg/ml)
Each mL contains Milrinone Lactate equivalent to Milrinone USP…. 1mg

3. DOSAGE FORM AND STRENGTH
Injection; 10mg/10 ml

4. CLINICAL PARTICULARS

4.1. Indications
Milrinone Lactate is indicated in short term treatment of severe congestive heart failure irresponsive in to conventional maintenance therapy and in acute heart failure including low output state following surgery.

4.2. Posology and Method of Administration

Posology
For intravenous administration.

Adults
Milrinone Lactate Injection should be given as a loading dose of 50 µg/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 1.13 mg/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 40 ml diluent per 10 ml ampoule (400 ml diluent per 100 ml** Milrinone Lactate Injection). 0.45% saline, 0.9% saline or 5% glucose may be used as diluents.

Milrinone Lactate Injection Dose (µg/kg/min)	Infusion Delivery 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

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 – 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. 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)	Milrinone Lactate Injection Dose (µg/kg/min)	Maintenance Infusion Delivery Rate (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 haemodynamic response.

Special populations
Elderly
Experience so far suggests that no special dosage recommendations are necessary.

Paediatric population
In published studies selected doses for infants and children were:
• Intravenous loading dose: 50 – 75 µg/kg administered over 30 – 60 minutes.

• Intravenous continuous infusion: To be initiated on the basis of hemodynamic response and the possible onset of undesirable effects between 0.25 – 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 have to be taken into consideration.

Renal impairment
Due to lack of data the use of milrinone is not recommended in paediatric population with renal impairment.

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.

Method of administration
Milrinone Lactate Injection should be administered with a loading dose followed by a continuous infusion (maintenance dose).

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

4.4. Special Warnings and Precautions for Use
General
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.

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

In neonates, following open heart surgery during Milrinone Lactate 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 paediatric 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 paediatric patients is still not clear, therefore the use of milrinone is not recommended in this population.

In paediatric 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 paediatric 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. In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in paediatric 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.

4.5. Drug Interactions
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.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Although animal studies have not revealed evidence of drug-induced fetal 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 fetus.

Breast-feeding
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.

Pediatric Use
Long-term safety data for paediatric population are not yet available.

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

Renal Impairment
See section 4.1. Posology and Method of Administration.

Hepatic Impairment
No information is available for usage of milrinone in hepatic impairment patients.

4.7. Effects on Ability to Drive and 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).

Adverse reaction	Frequency of adverse reaction
Blood and lymphatic system disorders	
Thrombocytopenia	Uncommon
Reduction of red blood count and/or haemoglobin concentration	Not known
Cardiac disorders	
Ventricular ectopic activity, Non sustained or sustained ventricular tachycardia, Supraventricular arrhythmias, Hypotension	Common
Ventricular fibrillation, Angina/chest pain	Uncommon
Torsades de pointes	Very rare
General disorders and administration site conditions	
Infusion site reaction	Not known
Hepatobiliary disorders	
Liver function tests abnormal	Uncommon
Immune system disorders	
Anaphylactic shock	Very rare
Metabolism and nutrition disorders	
Hypokalaemia	Uncommon
Nervous system disorders	

Adverse reaction	Frequency of adverse reaction
Headaches, usually mild to moderate in severity	Common
Tremor	Uncommon
Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Very rare
Skin and subcutaneous tissue disorders	
Skin reactions such as rash	Very rare
Renal and urinary disorders	
Renal failure, secondary to a concomitant hypotension.	Not known
Paediatric population	
Nervous system disorders	
Interventricular haemorrhage	Not known
Congenital, familial, and genetic disorders	
Patent ductus arteriosus***	Not known

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

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +91- 40 38265227 (Direct line); +91 7331134745 (WhatApp). By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose

Overdose of intravenous Milrinone Lactate 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

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

Mechanism of action

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

5.2. Pharmacokinetic Properties

Following intravenous injections of 12.5 – 125 µg/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 - 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/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.

Paediatric 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 paediatric population with normal renal function, steady-state milrinone plasma concentrations after 6 – 12 hours continuous infusion of 0.5 – 0.75 µg/kg/min were about 100 - 300 ng/ml.

Following intravenous infusion of 0.5 – 0.75 µg/kg/min to neonates, infants and children after open heart surgery, milrinone has a volume of distribution ranging from 0.35 – 0.9 L/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 L/kg.

Several pharmacokinetic studies showed that, in paediatric population, clearance increases with increasing age. Infants have significantly lower clearance than children (3.4 – 3.8 ml/kg/min versus 5.9 – 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 – 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 paediatric 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.

5.3 Pharmacodynamic Properties

Paediatric 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 – 75 µg/kg administered over 30 – 60 minutes followed by an intravenous continuous infusion of 0.25 – 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 paediatric use of milrinone in patients with nonhyperdynamic 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.

6. NONCLINICAL PROPERTIES

6.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

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 fetal rats. Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10 mg/kg, 1 mg/kg and 0.1 mg/kg). The dilating effects of milrinone in the fetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone (10 mg/kg, 1 mg/kg and 0.1 mg/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 fetal 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.

7. PHARMACEUTICAL PARTICULARS

7.1. Incompatibilities

Not applicable.

7.2. Packing Information

Clear tubular 10mL/20mm European blow back vial with 20 mm Bromobutyl serum rubber stopper and 20mm Aluminium flip off seals.

7.3. Storage and Handling Information

Store at 20°C to 25°C.

KEEP OUT OF REACH FOR CHILDREN

8. PATIENT COUNSELING INFORMATION

Not available

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

B33471-00

10. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

11. DATE OF REVISION

Oct. 2023