MILRICAN

MILRINONE LACTATE INJECTION

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

COMPOSITION

Each ml contains :

Milrinone lactate equivalent to Milrinone	1 mg
Water for injection IP	q.s.

DESCRIPTION

MILRICAN Injection, brand of milrinone lactate, is a member of a new class of bipyridine inotropic/ vasodilator agents with phosphodiesterase activity, distinct from digitalis glycisides or catecholamines. MILRICAN (milrinone lactate) is designated chemically as 1, 6-Dydro- 2-methyl-6-axo-[3.4'-bipyridine]-5-carbonitile lactate.

MILRICAN is available as sterile aqueous solutions of the lactate salt of milrinone for infection or infusion intravenously.

CLINICAL PHARMACOLOGY

Actions

MILRICAN is a positive inotrope and vasodilator, with little chronotropic activity, different in structure and mode of action from either the digitalis glucosides or catecholamines.

MILRICAN, at relevant inotropic and vasorelaxant concentrations, is a selective inhibitor of peak III cAMP phosphodiesterase isozyme in cardiac and vascular muscle. This inhibitory action is consistent with cAMP mediated increases in intracellular ionised calcium and contractile force in cardiac muscle, as well as with cAMP dependent contractile protein phosphorylation and relaxation in vascular muscle. Studies in normal subjects have shown that MILRICAN infection produces increases in the slope of the left ventricular pressure-dimension relationship, indicating a direct inotropic effect of the drug.

MILRICAN injection also produces dose-related and plasma concentration-related increases in forearm blood flow in patients with congestive heart failure, indicating a direct arterial vasodilator activitu of the drug.

Following intravenous loading, injections of 12.5 to 125.0 pg/kg to congestive heart failure patients, MILRICAN has a volume of distribution of 0.38 litres/kg, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 litres/kg/hr. Following intravenous infusions of 0.20 to 0.70 pg/kg/min to congestive heart failure patients, MILRICAN has a volume of distribution of about 0.45litres/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14litres/kg/hr. These pharmacokinetic parameters were not dose-dependent, and the area under the plasma concentration versus time curve following loading injections was significantly dose-dependent.

MILRICAN has been shown (by equilibrium dialysis) to be approximately 70% bound to human plasma protein.

The primary route of excretion of MILRICAN in man is via the urine, with much smaller amounts recovered in the faeces.

Elimination on 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 MILRICAN is approximately 0.3 litres/min while that of the metabolites is even greater, indicative of active secretion.

INDICATIONS

MILRICAN injection is indicated for the short term intravenous therapy of severe congestive heart failure. The majority of experience with intravenous MILRICAN has been in patients receiving digoxin and diuretics.

MILRICAN is also indicated for low output states following cardiac surgery, including weaning from cardio-pulmonary bypass pump.

DOSAGE AND ADMINISTRATION

MILRICAN injection should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:

LOADING DOSE

50mcg/kg Administer slowly over 10 minutes

MAINTENANCE DOSE

DOSE	**INFUSION RATE**	TOTAL DAILY
		(24 HOURS)
MINIMUM	0.375 mcg/kg/min	0.60 mg/kg
STANDARD	0.50 mcg/kg/min	0.77 mg/kg

NOTE: Administer as a continuous intravenous infusion.

The infusion rate should be adjusted according to haemodynamic and clinical response. Patients should be closely monitored. Most patients show an improvement in haemodynamic status as evidenced by increases in cardiac output and reductions in pulmonary capillary wedge pressure.

Dosage may be titrated to the maximum haemodynamic effect and should not exceed 1.13 mg/kg/day. Duration of therapy should depend upon patient responsiveness.

Preparations not used within 24 hours should be discarded.

Intravenous infusions of MILRICAN injection should be administered as described in the following chart.

MILRICAN injection (mcg/kg/min)	100 mcg/ml* (ml/kg/hr)	150 mcg/ml** (ml/kg/hr)	200 mcg/ml+ (ml/kg/hr)
0.375	0.22	0.15	0.11
0.400	0.24	0.16	0.12
0.500	0.30	0.20	0.15
0.600	0.36	0.24	0.18
0.700	0.42	0.28	0.21
0.750	0.45	0.30	0.2

In order to calculate flow rate (ml/hr) multiply infusion delivery rate by patient weight (in kg)

*Prepare by adding 90 ml diluent per 10 mg ampoule (10 ml) MILRICAN injection.

**Prepare by adding 57 ml diluent per 10 mg ampoule (10 ml) MILRICAN injection.

+Prepare by adding 40 ml diluent per 10 mg ampoule (10 ml) MILRICAN injection.

0.45% saline, 0.9% saline and 5% glucose may be used as diluents.

Note: Intravenous drug products should be inspected visually and should not be used if particulate matter or discolouration is present MILRICAN should not be diluted in sodium bicarbonate intravenous solution.

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. Reductions in the starting 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	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

SIDE EFFECTS

Cardiovascular Effects

Injection of MILRICAN increases ventricular ectopy, including nonsustained ventricular tachycardia. Life-threatening arrhythmias are infrequent and when present have been associated with certain underlying factors such as pre-existing arrhythmias,metabolic abnormalities (eg.hypokalaemia),abnormal digoxin levels and catheter insertion.

Very rarely cases of torsades de pointes have been reported.

Supraventricular arrhythmias were also reported.The incidence of both supraventricular and ventrucular arrhythmias has not been related to the dose or plasma level of milrinone. There is no evidencd for a patient subset which is at higher risk for ventricular arrhythmias.

Other cardiovascular adverse reactions include hypotension and angina/chest pain.

CNS Effects

Headaches, mostly mild to moderate in severity, have been reported.

Skin

Dermatological reactions such as rashes have been observed. Cases of infusion site reaction have been reported.

Liver

Abnormal liver function tests have been observed.

DRUG INTERACTIONS

No untoward clinical manifestations have been observed in whom MILRICAN injection was used concurrently with the following drugs: digitalis glycosides, lignocaine, quinidine, hydralazine, prazosin, isosorbide dinitrate, glyceryl trinitrate, chlorthalidone, frusemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, diazepam, insulin, and potassium supplements.

Chemical Interactions

There is an immediate chemical interaction which is evidenced by the formation of a precipitate when frusemide is injected into an intravenous line of an infusion of MILRICAN. Therefore frusemide or bumetanide should not be administered in intravenous lines containing MILRICAN.

MILRICAN shoukd not be diluted in sodium bicarbonate intravenous solution.

WARNINGS

Myocardial ischaemia or infarction may occur in patients following cardiac surgery. Should these events occur, care should be taken with the use of MILRICAN as information on the safety of MILRICAN under these circumstances is limited.

Use in Acute Myocardial Infarction

Use of inotropic agents such as milrinone during the acute phases of a myocardial infarction may lead to an undesirable increases in myocardial oxygen consumption (MVO_2). Milrinone has not increased MVO_2 in patients with chronic heart failure, however, until further clinical experience with this class of drugs is gained, MILRICAN is not recommened during the acute phase of post myocardial infarction.

PRECAUTIONS

Supraventricular and ventricular arrhythmias have been observed in the high-risk population treated. In some patients, MILRICAN has been shown to increase ventricular ectopy, including non-sustained ventricular tachcardia. Patients receiving MILRICAN injection should be closely monitored (including heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function) during infusion.

MILRICAN produces a slight shortening in A-V node conduction time, indicating a potential for an increased ventricular response rate in patients with atrial flutter/fibrillation which is not being controlled with digitalis therapy. In these patients, prior digitalisation or treatment with other agents to prolong A-V noce conduction time should be considered.

MILRICAN injection may induce hypotension as a consequence of its vasodilatory action. Caution should there fore be exercised in patients with hypotension prior to treatment or in those showing excessive decreases in blood pressure during therapy with milrinone lactate. In such case, the infusion should be stopped until the hypotensive effect has been resolved, then resumed at a lower rate if resumption is considered necessary.

If prior vigorous diuretic therapy is suspected to have caused significant decreases in cardiac filling pressure. MILRICAN injection should be cautiously administered with monitoring of blood pressure, heart rate and clinical symptomatology.

Cases of infusion site reaction have been reported with intravenous milrionone therapy. Consequently, careful monitoring of the infusion site should be maintained so as to avoid possible extravasation.

Use in Renal Impairment

In patients with severe renal impairment the dose should be adjusted

Use during Lactation

Caution should be exercised when MILRICAN is administered to nursing women since it is not known whether it is excreted in human milk.

CONTRAINDICATIONS

MILRICAN injection should not be used in patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis. MILRICAN injection should not be used in lieu of surgical relief of the obsturction. Like other inotropic agents, MILRICAN may aggravate outflow tract obstruction in theses conditions.

Hypersensitivity to bipyridines or any other ingredient in the formulation.

OVER DOSAGE

Doses of MILRICAN injection may induce hypotension because of its vasodilator effect. If this occurs, administration of MILRICAN 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.

STORAGE

Store at a temperature not exceeding 25°C. Protect from light. Do not freeze.

PRESENTATION

1 Ampoule of 10ml in box.

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