

## ▣ Milrinone Lactate Injection

### 1 mg milrinone/mL

#### Inotrope / Vasodilator

### ACTION AND CLINICAL PHARMACOLOGY

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

Milrinone, 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 ionized calcium and contractile force in cardiac muscle, as well as with cAMP-dependent contractile protein phosphorylation and relaxation in vascular muscle. Additional experimental evidence also indicates that it is not a beta-adrenergic agonist, nor does it inhibit sodium-potassium adenosine triphosphatase activity as do the digitalis glycosides.

Clinical studies in patients with congestive heart failure have shown that Milrinone Lactate Injection produces dose and plasma level-related increase in left ventricular dP/dt, increase in forearm blood flow indicating a direct arterial vasodilator activity of the drug, and improves diastolic function as evidenced by improvement in left ventricular diastolic relaxation.

Studies in normal subjects have shown that Milrinone Lactate Injection produces increases in the slope of the left ventricular pressure-dimension relationship, indicating a direct inotropic effect of the drug. Both the inotropic and vasodilatory effects have been observed over the therapeutic range of milrinone plasma concentrations of 100 - 300 ng/mL.

### Pharmacokinetics

Following intravenous loading injections of 12.5 to 125.0 µg/kg to congestive heart failure patients, intravenous milrinone had a volume of distribution of 0.38 L/kg, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 L/kg/hr. Following intravenous infusions of 0.20 to 0.70 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, while the area under the plasma concentration versus time curve following loading injections was significantly dose-dependent.

The steady-state milrinone plasma levels after approximately 6 - 12 hours of unchanging maintenance infusion of 0.50 µg/kg/min are approximately 200 ng/mL.

Milrinone has been shown (by ultracentrifugation) to be in excess of 70% bound to human plasma proteins at plasma concentrations of 70 - 400 ng/mL.

The primary route of excretion of milrinone in man is via the urine, with much smaller amounts recovered in the feces. The major urinary excretion products in man are milrinone (83%) and its O-glucuronide metabolite (12%). 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 while that of the metabolites is even greater, indicative of active secretion.

In patients with moderate to severe renal impairment, both  $C_{max}$  (210 ng/mL) and  $T_{max}$  (1.19 hr) were increased compared to subjects with normal renal function

(162 ng/mL and 0.64 hr, respectively). The half-life of milrinone increased from 0.94 hr in subjects with normal renal function to 1.71 hr in patients with moderate renal impairment and to 3.09 hr in patients with severe renal impairment.

### Pharmacodynamics

In patients with congestive heart failure, intravenous milrinone produces prompt, significant improvements in cardiac output, pulmonary capillary wedge pressure and vascular resistance without clinically significant increases in heart rate or myocardial oxygen consumption. Onset of action generally occurs within 5 to 15 minutes.

Improvement in left ventricular function and relief of congestive heart failure symptoms in patients with ischemic heart disease have been observed. The improvement has occurred without inducing symptoms or electrocardiographic signs of myocardial ischemia.

In studies in congestive heart failure patients, Milrinone Lactate Injection administered as a loading injection followed by a maintenance infusion produced the following pharmacodynamic changes:

DOSAGE REGIMEN						
Load- ing Dose (µg/kg)	Mainte- nance Infusion (µg/kg/min)	CI	PCWP	SVR	HR	MAP
Percent Change						
37.5	0.375	+25	-20	-17	+ 3	- 5
50.0	0.50	+38	-23	-21	+ 3	- 5
75.0	0.75	+42	-36	-37	+10	-17

Patients evaluated for 48 hours maintained improvements in hemodynamic function, with no evidence of diminished response (tachyphylaxis), and in a small number of patients no evidence of tachyphylaxis was seen for as long as 72 hours of infusion.

The duration of therapy should depend upon patient responsiveness. Patients have been maintained on infusion of milrinone up to five days.

Intravenous milrinone is effective in fully digitalized patients without affecting glycoside plasma levels.

Milrinone has been shown to enhance atrio-ventricular nodal conduction rate (see **PRECAUTIONS**).

### INDICATIONS AND CLINICAL USE

Milrinone Lactate Injection is indicated for the short-term management of severe congestive heart failure including low output states following cardiac surgery. The majority of experience with the drug has been in patients receiving digoxin and diuretics. In some patients, Milrinone Lactate Injection has been shown to increase ventricular ectopy (see **WARNINGS**).

### CONTRAINDICATIONS

Milrinone Lactate Injection is contraindicated in patients who are hypersensitive to it or to any of its ingredients.

### WARNINGS

Supraventricular and ventricular arrhythmias have been observed in the high risk population of congestive heart failure patients treated with Milrinone Lactate Injection. In using the drug, consideration should be given to the fact that, in some patients, Milrinone Lactate Injection has been associated with an increase in ventricular ectopy including ventricular tachycardia or fibrillation (see **ADVERSE REACTIONS**). The incidence of arrhythmias has not been shown to be related to the dose or plasma level of milrinone. Patients receiving Milrinone Lactate Injection should be closely monitored during infusion.

No clinical studies have been conducted in patients in the acute phase of post myocardial infarction. Until further clinical experience is gained, milrinone is not recommended in these patients.

### PRECAUTIONS

Milrinone Lactate Injection should not be used in lieu of surgical relief of the obstruction in patients with severe obstructive aortic or pulmonary valvular disease. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

Milrinone Lactate Injection has been shown to enhance AV nodal conduction rate, indicating a potential for an increased ventricular response rate in patients with atrial flutter/fibrillation which is not being controlled with digitalis therapy. Digitalisation of these patients should be considered prior to the administration of milrinone.

During therapy with Milrinone Lactate Injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decrease in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to Milrinone Lactate Injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Fluid and electrolyte changes and renal function should be carefully monitored during therapy with Milrinone Lactate Injection.

Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during milrinone administration.

### Use in Renally Impaired Patients

Data obtained from patients with severe renal impairment (creatinine clearance = 0 - 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 infusion rate may be necessary in patients with renal impairment (see **DOSAGE AND ADMINISTRATION**).

### Use in Elderly Patients

Experience so far suggests that no special dosage recommendations for the elderly patient are necessary.

### Use in Pregnancy

Milrinone did not appear to be teratogenic when administered intravenously to pregnant rats at doses up to 3 mg/kg/day or pregnant rabbits at doses up to 12 mg/kg/day, although an increase in resorption rate was apparent at both 8 and 12 mg/kg/day (intravenous) in the latter species.

There are no studies in pregnant women. Milrinone Lactate Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Use in Nursing Mothers

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

### Use in Children

Safety and effectiveness in children have not been established.

### Drug Interactions

No untoward clinical manifestations have been observed in patients in whom Milrinone Lactate Injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, hydralazine, prazosin, isosorbide dinitrate, nitroglycerin, chlorothalidone, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, diazepam, insulin, and potassium supplements.

### Chemical Interactions

Precipitation occurs immediately when furosemide is mixed with milrinone solution. Therefore, furosemide should not be administered in intravenous lines containing Milrinone Lactate Injection.

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

### Animal Toxicity

Oral and intravenous administration of toxic dosages of milrinone to rats and dogs resulted in myocardial degeneration/fibrosis and endocardial hemorrhage, principally affecting the left ventricular papillary muscles. Coronary vascular lesions characterized by periarterial edema and inflammation have been observed in dogs only. The myocardial/endocardial changes are similar to those produced by beta-adrenergic receptor agonists such as isoproterenol, while the vascular changes are similar to those produced by minoxidil and hydralazine. Doses within the recommended clinical dose range

(up to 1.13 mg/kg/day) for congestive heart failure patients have not produced significant adverse effects in animals.

### ADVERSE REACTIONS

In clinical trials involving 413 patients who received Milrinone Lactate Injection, the most frequent adverse effects observed were ventricular arrhythmias (12.6%) and the most severe adverse effect observed was ventricular fibrillation (0.2%).

Adverse reactions occurring in patients treated with Milrinone Lactate Injection are shown below in order of decreasing frequency:

Ventricular arrhythmias	12.6%
Ventricular ectopic activity	9.0%
Ventricular tachycardia	3.6%
Ventricular fibrillation	0.2%
Supraventricular arrhythmias	3.6%
Hypotension	3.1%
Headache	2.4%
Angina pectoris/Chest pain	1.4%
Hypokalemia	0.7%
Thrombocytopenia	0.5%
Tremor	0.5%

### SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific antidote to milrinone is known, but general measures for circulatory support should be taken. Milrinone Lactate Injection may produce hypotension because of its vasodilator effect. In case of overdose, administration of Milrinone Lactate Injection should be reduced or temporarily discontinued until the patient's condition stabilizes.

### DOSAGE AND ADMINISTRATION

#### General Information

- Prior correction or adjustment of fluid/electrolytes may be necessary to obtain a satisfactory response with Milrinone Lactate Injection (see **PRECAUTIONS**).
- Suitable diluents include Normal or Half Normal Saline Injection or sterile 5% Dextrose Injection.
- Diluted solutions should be used within 24 hours at room temperature or within 72 hours if refrigerated (2 - 8°C).
- Furosemide should not be added to Milrinone Lactate Injection due to a chemical interaction.

#### Drug 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 µg/kg; administered slowly over 10 minutes		
(For ease of administration, Milrinone Lactate Injection may be diluted with suitable diluents or used undiluted if suitable infusion equipment is available.)		
MAINTENANCE DOSE		
	Infusion Rate	Total Daily Dose (24 hours)
minimum	0.375 µg/kg/min	0.60 mg/kg
standard	0.50 µg/kg/min	0.77 mg/kg
maximum	0.75 µg/kg/min	1.13 mg/kg
Administer as a continuous intravenous infusion.		

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 reduction in pulmonary capillary wedge pressure. Dosage may be titrated to the maximum hemodynamic effect but should not exceed 1.13 mg/kg/day. Duration of therapy should depend upon patient responsiveness. Intravenous infusions of Milrinone Lactate Injection should be administered as described in the following chart.

INFUSION DELIVERY RATE			
Milrinone Lactate Dosage (µg/kg/min)	Concentration of Milrinone in Infusion		
	100 µg/mL*	150 µg/mL**	200 µg/mL†
	DELIVERY RATE		
	(mL/kg/hr)	(mL/kg/hr)	(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	0.22

In order to calculate flow rate (mL/hr), multiply infusion delivery rate by patient weight in kilograms.  
 \* Prepare by adding 180 mL diluent per 20 mg vial (20 mL) Milrinone Lactate Injection.  
 \*\*Prepare by adding 113 mL diluent per 20 mg vial (20 mL) Milrinone Lactate Injection.  
 † Prepare by adding 80 mL diluent per 20 mg vial (20 mL) Milrinone Lactate Injection.

#### Dosage Adjustment in Renally Impaired Patients

The loading dosage is not affected, but reductions in the maintenance infusion rate may be necessary according to the following table. (See **PRECAUTIONS, Use in Renally Impaired Patients.**)

Creatinine Clearance (mL/min/1.73 m <sup>2</sup> )	Milrinone Lactate (µg/kg/min)	Concentration of Milrinone in Infusion		
		100 µg/mL*	150 µg/mL**	200 µg/mL†
		DELIVERY RATE		
		(mL/kg/hr)	(mL/kg/hr)	(mL/kg/hr)
5	0.2	0.12	0.08	0.06
10	0.23	0.14	0.09	0.07
20	0.28	0.17	0.11	0.08
30	0.33	0.2	0.13	0.1
40	0.38	0.23	0.15	0.11
50	0.43	0.26	0.17	0.13

In order to calculate flow rate (mL/hr), multiply infusion delivery rate by patient weight in kilograms.

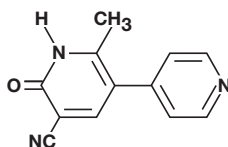
### PHARMACEUTICAL INFORMATION

#### Drug Substance

**Common Name:** Milrinone (USAN)  
Milrinone lactate is formed *in situ*.

**Chemical Name:** 1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile

#### Structural Formula:



**Molecular Formula:** C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O

**Molecular Weight:** 211.22

**Physical Form:** Milrinone is an off-white to tan crystalline powder.

**Solubility:** Milrinone is soluble in acidic and basic aqueous solutions. It is also soluble in chloroform and methanol, slightly soluble in dimethylformamide, and not soluble in ethanol and ethyl ether.

**pKa and pH values:** The pKa value is 9.67.  
The pH is 6.35.

#### Composition

Milrinone Lactate Injection is provided as a sterile, clear, colourless to pale yellow solution. The pH of Milrinone Lactate Injection is adjusted to between 3.2 and 4.0 with lactic acid or sodium hydroxide. Each mL contains milrinone lactate equivalent to 1 mg milrinone and anhydrous dextrose USP 47 mg, in Water for Injection. The total concentration of lactic acid can vary between 0.95 and 1.29 mg/mL.

### STABILITY AND STORAGE RECOMMENDATIONS

Store Milrinone Lactate Injection vials at room temperature (15 - 30°C). Avoid freezing.

#### Diluted Solutions

For ease of administration, Milrinone Lactate Injection may be diluted with suitable diluents such as Normal or Half Normal Saline Injection or sterile 5% Dextrose Injection, or may be used undiluted if suitable equipment is available.

Dilution as described under **DOSAGE AND ADMINISTRATION, Drug Administration.**

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration
20 mg vial (20 mL)	180 mL	200 mL	100 µg/mL
20 mg vial (20 mL)	113 mL	133 mL	150 µg/mL
20 mg vial (20 mL)	80 mL	100 mL	200 µg/mL

Diluted solutions should be used within 24 hours at room temperature (15 - 30°C) or 72 hours if refrigerated (2 - 8°C).

For detailed information regarding dilution, see **DOSAGE AND ADMINISTRATION.**

Precipitation occurs immediately when furosemide is mixed with milrinone solution. Therefore, furosemide should not be administered in intravenous lines containing Milrinone Lactate Injection.

**Note:** As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

### AVAILABILITY OF DOSAGE FORMS

Milrinone Lactate Injection is available in single-dose vials of 10 and 20 mL. Each mL contains milrinone lactate equivalent to 1 mg milrinone. The total concentration of lactic acid can vary between 0.95 and 1.29 mg/mL.

C601710 10 mL single-dose vials in packages of 10.

C601720 20 mL single-dose vials in packages of 10.

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