CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75830

DRAFT FINAL PRINTED LABELING

Faulding

Milrinone Lactate Injection

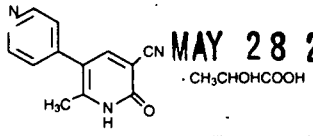
APPROVED

CODE 128 F.P.O.

SCAN BARS

DESCRIPTION

Milrinone Lactate Injection is a member of a new class of bipyridine inotropic/vasodilator agents with phosphodiesterase inhibitor activity, distinct from digitalis glycosides or catecholamines. Milrinone lactate is designated chemically as 1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile lactate and has the following structural formula:



MAY 28 2002

Milrinone is an off-white to tan crystalline compound with a molecular weight of 211.2 and a molecular formula of $C_{12}H_9N_3O$. It is slightly soluble in methanol, and very slightly soluble in chloroform and in water. As the lactate salt, it is stable and colorless to pale yellow in solution. Milrinone lactate is available as sterile aqueous solutions of the lactate salt of milrinone for injection or infusion intravenously.

Sterile single-dose vials of 10, 20, and 50 mL contain in each mL milrinone lactate equivalent to 1 mg milrinone and 47 mg Dextrose, Anhydrous, USP, in Water for Injection, USP. The pH is adjusted to between 3.2 and 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 0.95 mg/mL and 1.29 mg/mL. These vials require preparation of dilutions prior to administration to patients intravenously.

CLINICAL PHARMACOLOGY

Milrinone 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 milrinone 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 produces dose-related and plasma drug concentration-related increases in the maximum rate of increase of left ventricular pressure. Studies in normal subjects have shown that milrinone produces increases in the slope of the left ventricular pressure-dimension relationship, indicating a direct inotropic effect of the drug. Milrinone also produces dose-related and plasma concentration-related increases in forearm blood flow in patients with congestive heart failure, indicating a significantly decreased by 17 percent, 21 percent, and 37 percent. Mean arterial pressure fell by up to 5 percent at the two lower dose regimens, but by 17 percent at the highest dose. Patients evaluated for 48 hours maintained improvements in hemodynamic function, with no evidence of diminished response (tachyphylaxis). A smaller number of patients have received infusions of milrinone for periods up to 72 hours without evidence of tachyphylaxis.

The duration of therapy should depend upon patient responsiveness.

Milrinone has a favorable inotropic effect in fully digitalized patients without causing signs of glycoside toxicity. Theoretically, in cases of atrial flutter/fibrillation, it is possible that milrinone may increase ventricular response rate because of its slight enhancement of AV node conduction. In these cases, digitalis should be considered prior to the institution of therapy with milrinone.

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

The steady-state plasma milrinone concentrations after approximately 6 to 12 hours of unchanging maintenance infusion of 0.50 mcg/kg/min are approximately 200 ng/mL. Near maximum favorable effects of milrinone on cardiac output and pulmonary capillary wedge pressure are seen at plasma milrinone concentrations in the 150 ng/mL to 250 ng/mL range.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Milrinone lactate is contraindicated in patients who are hypersensitive to it.

WARNINGS:

Whether given orally or by continuous or intermittent intravenous infusion, milrinone has not been shown to be safe or effective in the longer (greater than 48 hours) treatment of patients with heart failure. In a multicenter trial of 1088 patients with Class III and IV heart failure, long-term oral treatment with milrinone was associated with no improvement in symptoms and an increased risk of hospitalization and death. In this study, patients with class IV symptoms appeared to be at particular risk of life-threatening

blood flow in patients with congestive heart failure, including a direct arterial vasodilator activity of the drug.

Both the inotropic and vasodilatory effects have been observed over the therapeutic range of plasma milrinone concentrations of 100 ng/mL to 300 ng/mL.

In addition to increasing myocardial contractility, milrinone improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation.

The acute administration of intravenous milrinone has also been evaluated in clinical trials in excess of 1600 patients, with chronic heart failure, heart failure associated with cardiac surgery, and heart failure associated with myocardial infarction. The total number of deaths, either on therapy or shortly thereafter (24 hours) was 15, less than 0.9%, few of which were thought to be drug-related.

Pharmacokinetics

Following intravenous injections of 12.5 mcg/kg to 125 mcg/kg to congestive heart failure patients, milrinone had a volume of distribution of 0.38 liters/kg, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 liters/kg/hr. Following intravenous infusions of 0.20 mcg/kg/min to 0.70 mcg/kg/min to congestive heart failure patients, the drug had a volume of distribution of about 0.45 liters/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14 liters/kg/hr. These pharmacokinetic parameters were not dose-dependent, and the area under the plasma concentration versus time curve following injections was significantly dose-dependent.

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

The primary route of excretion of milrinone in man is via the urine. The major urinary excretions of orally administered milrinone 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 liters/min, indicative of active secretion.

Pharmacodynamics:

In patients with heart failure due to depressed myocardial function, milrinone produced prompt dose and plasma concentration related increase in cardiac output and decreases in pulmonary capillary wedge pressure and vascular resistance, which were accompanied by mild-to-moderate increases in heart rate. Additionally, there is no increased effect on myocardial oxygen consumption. In uncontrolled studies, hemodynamic improvement, during intravenous therapy with milrinone was accompanied by clinical symptomatic improvement but the ability of milrinone to relieve symptoms has not been evaluated in controlled clinical trials. The great majority of patients experience improvements in hemodynamic function within 5 to 15 minutes of the initiation of therapy.

In studies in congestive heart failure patients, milrinone when administered as a loading injection followed by a maintenance infusion produced significant mean initial increases in cardiac index of 25 percent, 38 percent, and 42 percent at dose regimens of 37.5 mcg/kg/0.375 mcg/kg/min, 50 mcg/kg/0.50 mcg/kg/min, and 75 mcg/kg/0.75 mcg/kg/min, respectively. Over the same range of loading injections and maintenance infusions, pulmonary capillary wedge pressure significantly decreased by 20 percent, 23 percent, and 36 percent, respectively, while systemic vascular resistance

symptoms appeared to be at particular risk of life threatening **cardiovascular reactions. There is no evidence that milrinone given by long term continuous or intermittent infusion does not carry a similar risk.**

The use of milrinone both intravenously and orally has been associated with increased frequency of ventricular arrhythmias, including nonsustained ventricular tachycardia. Long-term oral use has been associated with an increased risk of sudden death. Hence, patients receiving milrinone should be observed closely with the use of continuous electrocardiographic monitoring to allow the prompt detection and management of ventricular arrhythmias.

PRECAUTIONS

General:

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

Supraventricular and ventricular arrhythmias have been observed in the high-risk population treated. In some patients, injections of milrinone and oral milrinone have been shown to increase ventricular ectopy, including non-sustained ventricular tachycardia. The potential for arrhythmia, present in congestive heart failure itself, may be increased by many drugs or combinations of drugs. Patients receiving milrinone should be closely monitored during infusion.

Milrinone Injection produces a slight shortening of AV node conduction time, indicating a potential for an increased ventricular response rate in patients with atrial flutter/fibrillation which is not controlled with digitalis therapy.

During therapy with milrinone, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

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

USE IN ACUTE MYOCARDIAL INFARCTION

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

Laboratory Tests - Fluid and Electrolytes- Fluid and electrolyte changes and renal function should be carefully monitored during therapy with milrinone. 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 use of milrinone.

Drug Interactions - No untoward clinical manifestations have been observed in limited experience with patients in whom milrinone was used concurrently with the following drugs: digitalis glycosides; lidocaine, quinidine; hydralazine, prazosin; isosorbide dinitrate, nitroglycerin; chlorthalidone, furosemide, hydrochlorothiazide, spironolactone; captopril; heparin, warfarin, diazepam, insulin; and potassium supplements.

Chemical Interactions - There is an immediate chemical

10 mL Single Dose Vial NDC 61703-242-32

Milrinone Lactate Injection

10 mg/10 mL

1 mg/mL*

For Intravenous Use Only

℞ only

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*Each mL contains milrinone lactate equivalent to 1 mg milrinone, and 47 mg dextrose, anhydrous, USP, in Water for Injection. pH adjusted between 3.2 and 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 0.95 mg/mL and 1.29 mg/mL. **Contains No Preservative.**

Usual Dosage: See package insert.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F)(see USP). Avoid freezing.

Manufactured for:
FAULDING PHARMACEUTICAL CO.
200 Elmora Avenue, Elizabeth, NJ 07207 USA
by: Faulding Puerto Rico, Inc.
P.O. Box 250471, Aguadilla, Puerto Rico 00604
PL076/HE 5/01

20 mL Single Dose Vial NDC 61703-242-21

Milrinone Lactate Injection

20 mg/20 mL

1 mg/mL*

For Intravenous Use Only

℞ only

MAY 28 2002

APPROVED

*Each mL contains milrinone lactate equivalent to 1 mg milrinone, and 47 mg dextrose, anhydrous, USP, in Water for Injection. pH adjusted between 3.2 and 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 0.95 mg/mL and 1.29 mg/mL. **Contains No Preservative.**

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P.O. Box 250471, Aguadilla, Puerto Rico 00604
PL076/HE 5/01

50 mL Single Dose Vial NDC 61703-242-50

Milrinone Lactate Injection

50 mg/50 mL

1 mg/mL*

For Intravenous Use Only

℞ only

APPROVED

*Each mL contains milrinone lactate equivalent to 1 mg milrinone, and 47 mg dextrose, anhydrous, USP, in Water for Injection. pH adjusted between 3.2 and 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 0.95 mg/mL and 1.29 mg/mL. **Contains No Preservative.**

Usual Dosage: See package insert.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F)(see USP). Avoid freezing.

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vary between 0.95 mg/mL and 1.29 mg/mL.
Contains No Preservative.

Usual Dosage: See package insert.

Discard any unused portion.

Store at controlled room temperature 15 C to 30 C (59 F to 86 F)(see USP).
Avoid freezing.

1 x 50 mL Vial NDC 61703-242-50

Milrinone Lactate Injection

50 mg/ 50 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vial

Faulding

Milrinone Lactate Injection

50 mg/ 50 mL

1 mg/mL*

Faulding

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61703-242-50

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UC040/HE 5/01

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1 x 50 mL Vial NDC 61703-242-50

Milrinone Lactate Injection

50 mg/ 50 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vial

Faulding

UNVARNISHED AREA

■ Blue PANTONE 308 CV
■ Blue PANTONE 295 CV

SIZE: 1 7/8 x 1 7/8 x 3 1/8

Faulding

61703-242-21

Milrinone Lactate Injection

20 mg/20 mL

1 mg/mL*

10 x 20 mL Vials NDC 61703-242-21

Milrinone Lactate Injection

20 mg/20 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vials

Faulding

*Each mL contains milrinone lactate equivalent to 1 mg milrinone, and 47 mg dextrose, anhydrous, USP, in Water for Injection. pH adjusted between 3.2 and 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 0.95 mg/mL and 1.29 mg/mL. **Contains No Preservative.**

Usual Dosage: See package insert.

Discard any unused portion.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F)(see USP). Avoid freezing.

10 x 20 mL Vials NDC 61703-242-21

Milrinone Lactate Injection

20 mg/20 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vials

Faulding

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SC076/HE 5/01

Faulding

PMS COLORS
Blue PANTONE 307 CV
Blue PANTONE 295 CV

6 L x 2 7/16 W x 2 5/8 H

10 x 10 mL Vials

NDC 61703-242-32

Milrinone Lactate Injection

10 mg/10 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vials

UNVARNISHED AREA

Faulding

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10 x 10 mL Vials

NDC 61703-242-32

Milrinone Lactate Injection

10 mg/10 mL

1 mg/mL*

For Intravenous Use Only

℞ only

Single Dose Vials

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SC075/HE 5/01

Faulding

Milrinone Lactate Injection

10 mg/10 mL

1 mg/mL*

61703-242-32

Faulding

PMS COLORS
Blue PANTONE 306 CV
Blue PANTONE 295 CV

4 11/16 L x 1 15/16 W x 2 3/16 H