MILRINONE (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾CV052

Commonly used brand name(s):Primacor.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Cardiotonic.

Indications

Accepted

Congestive heart failure (treatment)¾Milrinone is indicated for the short-term management of congestive heart failure. 1 Milrinone has been used primarily in patients concurrently receiving digoxin and diuretics. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾211.22 2

Mechanism of action/Effect:

Milrinone is a phosphodiesterase inhibitor that has direct positive inotropic and vasodilatory actions. 1, 3, 4, 14 Milrinone increases cardiac contractility which results in an increase in cardiac output 1.

Milrinone also relaxes both arterial and venous smooth muscle, thereby reducing both preload and afterload. 3, 4, 7 These effects are mediated by an increase in cytoplasmic cyclic adenosine monophosphate (cAMP) resulting from phosphodiesterase III inhibition in cardiac and smooth muscle. 1, 3, 4, 5, 14

Other actions/effects:

Milrinone slightly increases atrioventricular (AV) conduction velocity. 3 Milrinone may also have a favorable effect on ventricular diastolic function. 5, 6, 13

Protein binding:

High (70%). 1, 13

Half-life:

Elimination¾2.3 to 2.7 hours. 1, 13, 15 Elimination half-life is significantly increased in patients with renal function impairment 1.

Duration of action:

3 to 6 hours. 13

Elimination:

Renal. 1

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to amrinone may also be sensitive to milrinone.

Carcinogenicity

Twenty-four-month oral administration of milrinone to mice at doses of up to 40 mg per kg of body weight (mg/kg) per day (50 times the human oral therapeutic dose in a 50 kg patient) or to rats at doses of up to 5 mg/kg per day (about 6 times the human oral therapeutic dose) did not reveal carcinogenic potential. 1

Mutagenicity

Positive results were observed in the presence of a metabolic activation system with the Chinese hamster ovary chromosome aberration assay. 1 However, negative results were observed in the Ames test, mouse lymphoma assay, micronucleus test, and the in vivo rat bone marrow metaphase analysis. 1

Pregnancy/Reproduction

Fertility¾No effect on male or female fertility was observed when milrinone was studied in rats at oral doses of up to 32 mg/kg per day. 1

Pregnancy¾Adequate and well-controlled studies have not been done in humans.
Studies in pregnant rats and rabbits given milrinone during organogenesis revealed no evidence of teratogenicity at oral doses of up to 40 mg/kg per day and 12 mg/kg per day, respectively. 1 Lack of teratogenic effect was also observed in rats and rabbits given milrinone intravenously at doses of up to 3 mg/kg per day and 12 mg/kg per day, respectively. 1 However, an increased resorption rate was observed in rabbits at doses at or above 8 mg/kg per day. 1

FDA Pregnancy Category C. 1

Breast-feeding

It is not known whether milrinone is distributed into breast milk. 1

Pediatrics

No information is available on the relationship of age to the effects of milrinone in pediatric patients. Safety and efficacy have not been established.

Geriatrics

Although appropriate studies on the relationship of age to the effects of milrinone have not been performed in the geriatric population, patients given milrinone in clinical trials included patients up to 80 years of age (mean age 57 to 61). 1, 8, 9, 10 These trials have not demonstrated geriatrics-specific problems that would limit the usefulness of milrinone in the elderly. 1, 8, 9, 10 However, elderly patients are more likely to have age-related renal function impairment, which may require adjustment of dosage in patients receiving milrinone.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Hypotension-producing medications (see Appendix II)

(concurrent use with milrinone may produce additive hypotensive effects)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hypersensitivity to milrinone 1

Risk-benefit should be considered when the following medical problems exist

>> Aortic or pulmonic valve disease, severe, including 1

Hypertrophic subaortic stenosis 1

(inotropic agents, such as milrinone, should not be used as a substitute for surgery in patients with aortic or pulmonic valve disease 1 ; in patients with hypertrophic subaortic stenosis, inotropic agents may aggravate left ventricular outflow tract obstruction 1)

>> Myocardial infarction, acute

(clinical studies have not been done in patients with acute myocardial infarction; use of milrinone in these patients is not recommended 1)

Renal function impairment

(milrinone elimination is reduced in these patients; a dosage adjustment may be necessary 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Blood pressure and

>> Heart rate

(determinations recommended at periodic intervals; milrinone infusion should be slowed or stopped if an excessive fall in blood pressure occurs 1)

>> Body weight/fluid status 1 and

>> Renal function determinations 1 and

>> Electrolyte, especially potassium, concentrations 1 , serum

(careful monitoring is recommended; hypokalemia due to excessive diuresis may increase the risk of arrhythmias in patients taking digitalis glycosides 1)

>> Cardiac index 1 and

Central venous pressure and

>> Pulmonary capillary wedge pressure (PCWP) 1

(in most patients, milrinone administration increases cardiac output and reduces PCWP, signs of improved hemodynamics 1)

Electrocardiogram (ECG), continuous 16

(recommended throughout infusion period to monitor for potential arrhythmias)

Platelet counts

(recommended prior to initiation of therapy and at periodic intervals during milrinone therapy)

Side/Adverse Effects

Although milrinone has not been shown to be arrhythmogenic electrophysiologically, supraventricular and ventricular arrhythmias have occurred in patients treated with milrinone 1.

In some patients, milrinone has been shown to increase ventricular ectopic beats, including nonsustained ventricular tachycardia 1.

Milrinone slightly decreases atrioventricular (AV) nodal conduction time, which may cause an increase in the ventricular response rate in patients with atrial flutter or atrial fibrillation if the rate is not controlled with digitalis therapy 1.

In clinical trials, ventricular arrhythmias were reported in 12.1% of patients (2 patients experienced more than one type of arrhythmia): ventricular ectopic activity¾8.5%; nonsustained ventricular tachycardia¾2.8%; sustained ventricular tachycardia¾1%; and ventricular fibrillation¾0.2% 1.

Life-threatening arrhythmias, although infrequent, have occurred with milrinone therapy and have been associated with underlying conditions, such as pre-existing arrhythmias, hypokalemia or other metabolic abnormalities, abnormal digoxin levels, and catheter insertion 1.

Supraventricular arrhythmias have been reported in 3.8% of patients receiving milrinone 1.

The incidence of supraventricular and ventricular arrhythmias does not appear to be dose-related 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Arrhythmias 1, 9, 11, 12; hypotension 1, 13

Incidence rare

Angina 1, 13; thrombocytopenia 1, 9, 13

Note: Thrombocytopenia has been reported in approximately 0.4% of patients; 1 in some cases, decreases in platelet counts were judged to be only possibly related to milrinone therapy. 9

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Headache 1, 13

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effect has been selected on the basis of its potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Hypotension
Treatment of overdose

Treatment of overdose consists of general measures for circulatory support. 1

General Dosing Information

Pretreatment with digitalis is recommended in patients with atrial flutter or atrial fibrillation since milrinone's slight enhancement of atrioventricular (AV) conduction may increase ventricular response rates 1.

Patients who have received vigorous diuretic therapy may need cautiously liberalized fluid and electrolyte intake to ensure an adequate cardiac filling pressure for response to milrinone 1.

Caution is recommended to avoid extravasation of milrinone infusion.
It is recommended that a calibrated electronic infusion device be used to administer milrinone 1.

Parenteral Dosage Forms

Note: The available dosage form contains milrinone lactate, but dosages and strengths are expressed in terms of the base.

MILRINONE INJECTION

Usual adult dose

Congestive heart failure¾
Milrinone should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:
Loading dose: Intravenous, 50 mcg (0.05 mg) (base) per kg of body weight, administered slowly over ten minutes 1.

The following table provides the loading dose volume (mL) of milrinone injection (1 mg/mL) for a given patient body weight (kg) 1 :

Loading dose volume (mL) using 1 mg/mL concentration for a given patient body weight (kg)

Patient body weight (kg)	30	40	50	60	70	80	90	100	110	120

Loading dose (mL)	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6

Maintenance dose: Intravenous infusion, continuous:

	Infusion rate (mcg/kg/min)	Total daily (24 hour) dose (mg /kg)
Minimum	0.375	0.59
Standard	0.5	0.77
Maximum	0.75	1.13

The infusion rate should be adjusted according to the patient's hemodynamic and clinical response 1.

Milrinone drawn from vials should be diluted prior to maintenance dose administration 1.

The maintenance dose in mL per hour by patient body weight (kg) may be determined by referencing one of the following three tables:

	Milrinone infusion rate (mL/hr) using 100 mcg/mL concentration									
Maintenance dose (mcg/kg /min)	Patient body weight (kg)									
	30	40	50	60	70	80	90	100	110	120
0.375	6.8	9	11.3	13.5	15.8	18	20.3	22.5	24.8	27
0.4	7.2	9.6	12	14.4	16.8	19.2	21.6	24	26.4	28.8
0.5	9	12	15	18	21	24	27	30	33	36
0.6	10.8	14.4	18	21.6	25.2	28.8	32.4	36	39.6	43.2
0.7	12.6	16.8	21	25.2	29.4	33.6	37.8	42	46.2	50.4
0.75	13.5	18	22.5	27	31.5	36	40.5	45	49.5	54

	Milrinone infusion rate (mL/hr) using 150 mcg/mL concentration									
Maintenance dose (mcg/kg /min)	Patient body weight (kg)									
	30	40	50	60	70	80	90	100	110	120
0.375	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
0.4	4.8	6.4	8	9.6	11.2	12.8	14.4	16	17.6	19.2

0.5	6	8	10	12	14	16	18	20	22	24
0.6	7.2	9.6	12	14.4	16.8	19.2	21.6	24	26.4	28.8
0.7	8.4	11.2	14	16.8	19.6	22.4	25.2	28	30.8	33.6
0.75	9	12	15	18	21	24	27	30	33	36

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	10.1	11.3	12.4	13.5
0.4	3.6	4.8	6	7.2	8.4	9.6	10.8	12	13.2	14.4
0.5	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
0.6	5.4	7.2	9	10.8	12.6	14.4	16.2	18	19.8	21.6
0.7	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21	23.1	25.2
0.75	6.8	9	11.3	13.5	15.8	18	20.3	22.5	24.8	27

Note: In patients with renal function impairment, infusion rates may need to be reduced to compensate for a prolonged elimination half-life 1.

The following infusion rates are recommended:

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

Usual adult prescribing limits

1.13 mg (base) per kg of body weight per day. 1 Duration of therapy should depend upon patient responsiveness 1.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾1 mg (base [as the lactate]) per mL (Rx)[Primacor (available in 10- and 20-mL single-dose vials and 5-mL cartridges)] 1

200 mcg (base [as the lactate]) per mL in 5% dextrose injection (Rx)[Primacor (available in 100- and 200-mL flexible containers)] 1

Canada¾1 mg (base [as the lactate]) per mL (Rx)[Primacor (available in 10- and 20-mL single-dose vials)] 17

Packaging and storage:

Vials and cartridges of milrinone should be stored at controlled room temperature, between 15 and 30 °C (59 and 86 °F) 1.

Flexible containers should be stored at room temperature, 25 °C (77 °F); however, brief exposure to temperatures up to 40 °C (104 °F) does not adversely affect the product 1.

Protect either product from excessive heat and freezing 1.

Preparation of dosage form:

When given as a loading dose, milrinone drawn from vials may be administered undiluted, although diluting to a rounded total volume of 10 or 20 mL may simplify the visualization of the injection rate 1.

When given as a maintenance dose, milrinone drawn from vials should be diluted 1.

Milrinone may be diluted with 0.45% or 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP 1.

The table below shows the volume of diluent that must be used to achieve concentrations recommended for infusion:

Desired infusion concentration (mcg/mL)	Volume (mL) of milrinone 1 mg/mL	Volume (mL) of diluent	To make a total volume (mL) of
100	10	90	100
100	20	180	200
150	10	56.7	66.7
150	20	113	133
200	10	40	50
200	20	80	100

Milrinone in 100 mL and 200 mL flexible containers (200 mcg/mL in 5% dextrose injection) need not be diluted prior to use 1.

Stability:

Milrinone injection should not be used if particulate matter is present or the solution is discolored 1.

Incompatibilities:

Milrinone should not be administered in intravenous lines containing furosemide, since an immediate precipitate is formed. 1 Supplementary medication should not be added to milrinone flexible containers 1.