1 MILRINONE-BAXTER (1mg/mL, concentrate for injection)

MILRINONE-BAXTER (as lactate) 10mg/10mL concentrate for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Each single-dose ampoule of MILRINONE-BAXTER contains milrinone lactate equivalent to milrinone 10mg/10mL with anhydrous glucose (47mg/mL) in water for injections.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for injection.

MILRINONE-BAXTER is a sterile, clear, colourless to pale yellow aqueous solution, practically free from visible particles.

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 and 1.29mg/mL.

MILRINONE-BAXTER requires dilution prior to administration to patients intravenously.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Dose and method of administration

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

Loading Dose 50µg/kg administer slowly over 10 minutes		
Maintenance Dose		
	Infusion Rate	Total Daily Dose (24 hours)
Minimum	0.375µg/kg/min	0.60mg/kg
Standard	0.50µg/kg/min	0.77mg/kg
Maximum	0.75µg/kg/min	1.13mg/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.

Note: See *Dosage adjustment in renally impaired patients.*

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

Intravenous infusions of milrinone should be administered as described in the following table.

MILRINONE-BAXTER - Rates of infusion for concentrations of 100µg/mL, 150µg/mL and 200µg/mL Infusion delivery rate			
Milrinone (µg/kg/min)	100µg/mL (mL/kg/hr)	150µg/mL (mL/kg/hr)	200µg/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	0.22

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

The ampoules require preparation of dilutions prior to administration to patients intravenously. For instructions on dilution of the medicine before administration, see section 6.6.*Dosage adjustment in renally impaired patients*

Data obtained from patients with severe renal impairment (creatinine clearance = 0 to 30mL/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 (µg/kg/min)
5	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

4.3 Contraindications

- MILRINONE-BAXTER should not be used in patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis.
- MILRINONE-BAXTER should not be used in lieu of surgical relief of the obstruction.
- Like other inotropic agents, milrinone may aggravate outflow tract obstruction in these conditions.
- Hypersensitivity to milrinone, other bipyridines or any other ingredient in the formulation listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

Myocardial ischaemia or infarction may occur in patients following cardiac surgery. Should these events occur, care should be taken with the use of milrinone as information on the safety of milrinone 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 increase 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, milrinone is not recommended 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, milrinone has 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 (including heart rate, clinical state, electrocardiogram, fluid balance, electrolytes and renal function) during infusion.

Milrinone 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 node conduction time should be considered.

Milrinone may induce hypotension as a consequence of its vasodilatory action. Caution should therefore be exercised in patients with hypotension prior to treatment or in those showing excessive decreases in blood pressure during therapy with milrinone. In such cases, 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, milrinone should be cautiously administered with monitoring of blood pressure, heart rate, and clinical symptomatology.

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 intravenous milrinone therapy (see section 4.8). Consequently, careful monitoring of the infusion site should be maintained so as to avoid possible extravasation.

Effects on laboratory tests

Fluid and electrolyte changes, as well as serum creatinine levels, and renal function should be carefully monitored during milrinone therapy. Improvement in cardiac output with resultant 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 MILRINONE-BAXTER use.

Use in the elderly

There are no special dosage recommendations for the elderly patients. Ninety percent of all patients administered milrinone in clinical studies were within the age range of 45-70 years, with a mean age of 61 years. Patients in all age groups demonstrated clinically and statistically significant responses. No age-related effects on the incidence of adverse reactions have been observed.

Controlled pharmacokinetic studies have not disclosed any age-related effects on the distribution and elimination of milrinone.

Use in renal impairment

In patients with severe renal impairment the dose should be adjusted (see section 4.2).

Paediatric use
Safety and effectiveness in children have not been established.

4.5 Interaction with other medicines and other forms of interaction
No untoward clinical manifestations have been observed in patients in whom milrinone was used concurrently with the following drugs: digitalis glycosides, lidnocaine, quinidine, hydralazine, prazosin, isosorbide dinitrate, glyceryl trinitrate, chlortalidone, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, diazepam, insulin, and potassium supplements. See section 6.2 for further incompatibility information.

4.6 Fertility, pregnancy and lactation
Fertility
In reproductive performance studies in rats, milrinone had no effect on male or female fertility at oral doses up to 32 mg/kg/day.

Pregnancy (Category B3)
Oral administration of milrinone to pregnant rats and rabbits during organogenesis produced no evidence of teratogenicity at dose levels up to 40mg/kg/day and 12mg/kg/day respectively. Milrinone did not appear to be teratogenic when administered intravenously to pregnant rats at doses up to 3mg/kg/day or pregnant rabbits at doses up to 12mg/kg/day, although an increased resorption rate was apparent at dose levels above 3mg/kg/day (intravenous) in the latter species. There are no adequate and well-controlled studies in pregnant women. MILRINONE-BAXTER should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

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
Cardiovascular Effects
Ventricular arrhythmias were reported in 12.1% of patients receiving milrinone:
ventricular ectopic activity, 8.5%; non-sustained ventricular tachycardia, 2.8%; sustained ventricular tachycardia 1% and ventricular fibrillation, 0.2%. Holter recordings have demonstrated in some patients that injection of milrinone 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 (e.g. hypokalaemia), abnormal digoxin levels and catheter insertion.

Very rarely (< 0.01%) cases of torsades de pointes have been reported.

Supraventricular arrhythmias were reported in 3.8% of the patients receiving milrinone. The incidence of both supraventricular and ventricular arrhythmias has not been related to the dose or plasma level of milrinone. There is no evidence for a patient subset which is at higher risk for ventricular arrhythmias.

Other cardiovascular adverse reactions include hypotension 2.9% and angina/chest pain 1.2%.

CNS Effects
Headaches, mostly mild to moderate in severity, have been reported in 2.9% of patients receiving milrinone.

Skin
Dermatological reactions such as rashes have been observed in < 0.01% of patients. Cases of infusion site reaction have been reported.

Liver
Abnormal liver function tests have been observed in < 1% of patients.

Congenital, Familial and Genetic Disorders
Patent ductus arteriosus has been reported.

Renal and Urinary Disorders
Renal failure, secondary to a concomitant hypotension, has been reported.

Other Effects
Other adverse reactions reported, all with an incidence of less than 1% but not definitely related to the administration of milrinone include hypokalaemia, tremor, and thrombocytopenia.

Very rarely (< 0.01%) bronchospasm and anaphylactic shock have occurred.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose
Doses of milrinone may induce hypotension because of its vasodilator effect. If this occurs, administration of milrinone 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on: 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group
Cardiovascular system, cardiac therapy, cardiac stimulants excl, cardiac glycosides, phosphodiesterase inhibitors.

ATC code
C01CE02.

Mechanism of Action

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 ionised 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 β-adrenergic agonist, and unlike digitalis glycosides, it does not inhibit Na^+/K^+ ATPase activity.

Clinical studies in patients with congestive heart failure have shown that milrinone produces dose-related and plasma level-related increases in the maximum rate of increase of left ventricular pressure (dP/dt max). 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 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 100ng/mL to 300ng/mL.

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

Pharmacodynamic effects

In patients with depressed myocardial function, milrinone produces a prompt increase in cardiac output and decreases in pulmonary capillary wedge pressure and vascular resistance, without a significant increase in heart rate or myocardial oxygen consumption.

These haemodynamic improvements are both dose and plasma milrinone concentration related. Haemodynamic improvement during intravenous therapy with milrinone was accompanied by clinical symptomatic improvement, as measured by changes in New York Heart Association classification. The great majority of patients experience improvements in haemodynamic 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 as follows:

Cardiac Index	Loading Injection (µg/kg)	Maintenance Infusion (µg/kg/min)
25	37.5	0.375
38	50	0.500
42	75	0.750

Over the same range of loading injections and maintenance infusions, pulmonary capillary wedge pressure significantly decreased by 20%, 23% and 36%, respectively, while systemic vascular resistance significantly decreased by 17%, 21% and 37%. The heart rate was generally unchanged (increases of 2%, 3% and 10%, respectively). Mean arterial pressure fell by up to 5%, at the two lower dose regimens, but by 17% at the highest dose. Patients evaluated for 48 hours maintained

improvements in haemodynamic 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.

Milrinone has a favourable inotropic effect in fully digitalised 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 of milrinone.

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

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

Clinical efficacy and safety

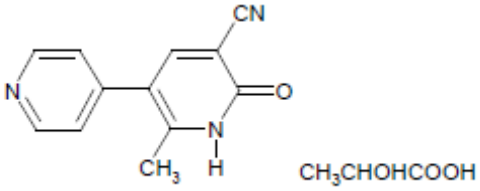
In a double-blind, placebo controlled study in patients being weaned off cardiopulmonary bypass, 100% of patients taking milrinone were successfully weaned off bypass compared to 33% of the placebo arm patients. All patients who initially failed blinded placebo treatment were successfully weaned from cardiopulmonary bypass support following administration with open-label milrinone.

In acute states following cardiac surgery, it is unlikely that treatment need be maintained for more than 12 hours.

Physicochemical Properties

Milrinone (as lactate), is a member of a new class of bipyridine inotropic/vasodilator agents with phosphodiesterase activity, distinct from digitalis glycosides or catecholamines.

The chemical name is 1,6-dihydro-2-methyl-6-oxo-[3,4'- bipyridine]-5-carbonitrile lactate and has the following structure:



Milrinone is an off-white to tan crystalline compound with molecular weights of 211.2 (milrinone), 301.3 (milrinone lactate). The empirical formula are $C_{12}H_9N_3O$ (milrinone), $C12H_9N_3O.(C_3H_6O_3)_X$ (milrinone lactate). Milrinone is stable and colourless to pale yellow in solution.

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

The CAS number is 78415-72-2 (milrinone), 100286-97-3 (milrinone lactate).

5.2 Pharmacokinetic properties

Distribution

Following intravenous loading, injections of 12.5 to 125.0µg/kg to congestive heart failure patients, milrinone 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 0.70µg/kg/min to congestive heart failure patients, milrinone has a volume of distribution of about 0.45 litres/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14 litres/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.

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

Biotransformation

The primary route of excretion of milrinone in man is via the urine, with much smaller amounts recovered in the faeces. The major urinary excretion products in man are milrinone (83%) and its o-glucuronide metabolite (12%).

Elimination

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 litres/min while that of the metabolites is even greater, indicative of active secretion.

5.3 Preclinical safety data

Carcinogenicity

Twenty-four months of oral administration of milrinone to mice at doses up to 40mg/kg/day was unassociated with evidence of carcinogenic potential. Neither was there evidence of carcinogenic potential when milrinone was orally administered to rats at doses up to 5mg/kg/day for 24 months or at 25mg/kg/day for up to 18 months in males and 20 months in females.

Genotoxicity

Whereas the Chinese Hamster Ovary Chromosome Aberration Assay was positive in the presence of a metabolic activation system, results from the Ames Test, the Mouse Lymphoma Assay, the Micronucleus Test and the *in vivo* Rat Bone Marrow Metaphase Analysis indicated an absence of mutagenic potential.

Animal toxicity

Oral and intravenous administration of toxic dosages of milrinone to rats and dogs resulted in myocardial degeneration/fibrosis and endocardial haemorrhage, principally affecting the left ventricular papillary muscles. Coronary vascular lesions characterised by periarterial oedema and inflammation have been observed in dogs only. The myocardial/endocardial changes are similar to those produced by β-adrenergic receptor agonists such as isoprenaline, while the vascular changes are similar to those produced by minoxidil and hydralazine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose, lactic acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

6.2 Incompatibilities

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

MILRINONE-BAXTER should not be diluted in sodium bicarbonate intravenous solution.

Compatibility studies with the diluents were conducted in non-PVC (polypropylene) bags.

6.3 Shelf life

24 months from date of manufacture.

Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbiological hazards. Preparations not used within 24 hours should be discarded.

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

From a microbiological point of view, the diluted solution should be used immediately. To reduce microbiological hazard, use as soon as practicable after dilution. Contains no antimicrobial preservative. For single use in one patient on one occasion only. Discard any remaining residue.

6.5 Nature and contents of container

MILRINONE-BAXTER 10mg/10mL is available in glass ampoules in packs of 5 and 10 ampoules.

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

Use the following calculations for preparation of infusions.

0.45% sodium chloride injection, 0.9% sodium chloride injection and 5% glucose injection may be used as diluents.

	Quantity of diluent per 10mg/10mL ampoule
100µg/mL	90mL
150µg/mL	57mL
200µg/mL	40mL

Note: Intravenous drug products should be inspected visually and should not be used if particulate matter or discolouration is present.

MILRINONE-BAXTER should not be diluted in sodium bicarbonate intravenous solution.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

MILRINONE-BAXTER is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
12 November 2015.

10 DATE OF REVISION OF THE TEXT

8 January 2026.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Hypersensitivity to milrinone included as contraindication.
4.5 & 6.2	Spelling correction.
4.8	url corrected.
4.9	Contact details updated.
8	Section updated.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.