1 MILRINONE-CLARIS (as lactate) 10 mg/mL concentrate for injection
Milrinone-Claris (as lactate) 10 mg/10mL concentrate for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Milrinone-Claris is a sterile, clear, colourless to pale yellow aqueous solution, practically free from visible particles, containing milrinone lactate equivalent to milrinone 10 mg/10 mL with anhydrous glucose (47 mg/mL) in water for injections. 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 1.29 mg/mL.
Milrinone-Claris requires dilution prior to administration to patients intravenously.

3 PHARMACEUTICAL FORM
Concentrate for injection.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Milrinone-Claris 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-Claris 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-Claris should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg/kg administer slowly over 10 minutes</td>
<td>Total Daily Dose (24 hours)</td>
</tr>
<tr>
<td>Infusion Rate</td>
<td>Minimum 0.375 µg/kg/min</td>
</tr>
<tr>
<td>Total Daily Dose (24 hours)</td>
<td>0.60 mg/kg</td>
</tr>
</tbody>
</table>

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 1.13 mg/kg/day. Duration of therapy should depend upon patient responsiveness.

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. Compatibility studies with the diluents were conducted in non-PVC (polypropylene) bags. Intravenous infusions of milrinone should be administered as described in the following chart.
MILRINONE - RATES OF INFUSION
FOR CONCENTRATIONS OF 100 µg/mL, 150 µg/mL and 200 µg/mL INFUSION DELIVERY RATE

<table>
<thead>
<tr>
<th>Milrinone (µg/kg/min)</th>
<th>100 µg/mL (mL/kg/hr)</th>
<th>150 µg/mL (mL/kg/hr)</th>
<th>200 µg/mL (mL/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.375</td>
<td>0.22</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>0.400</td>
<td>0.24</td>
<td>0.16</td>
<td>0.12</td>
</tr>
<tr>
<td>0.500</td>
<td>0.30</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>0.600</td>
<td>0.36</td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td>0.700</td>
<td>0.42</td>
<td>0.28</td>
<td>0.21</td>
</tr>
<tr>
<td>0.750</td>
<td>0.45</td>
<td>0.30</td>
<td>0.22</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Quantity of diluent per 10 mg/10 mL ampoule</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 µg/mL</td>
</tr>
<tr>
<td>150 µg/mL</td>
</tr>
<tr>
<td>200 µg/mL</td>
</tr>
</tbody>
</table>

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

Milrinone-Claris 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:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min/1.73m²)</th>
<th>Infusion Rate (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.20</td>
</tr>
<tr>
<td>10</td>
<td>0.23</td>
</tr>
<tr>
<td>20</td>
<td>0.28</td>
</tr>
<tr>
<td>30</td>
<td>0.33</td>
</tr>
<tr>
<td>40</td>
<td>0.38</td>
</tr>
<tr>
<td>50</td>
<td>0.43</td>
</tr>
</tbody>
</table>
4.3 Contraindications

- Milrinone-Claris should not be used in patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis.
- Milrinone-Claris 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 bipyridines or any other ingredient in the formulation.

4.4 Special warnings and precautions for use

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 (MVO₂). Milrinone has not increased MVO₂ 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.

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 Adverse Effects). 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 (see Dosage and Administration).

Paediatric Use

Safety and effectiveness in children have not been established.
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.

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-Claris use.

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, lignocaine, quinidine, hydralazine, prazosin, isosorbide dinitrate, glyceryl trinitrate, chlorothalidone, 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 milrinone. Therefore frusemide or bumetanide should not be administered in intravenous lines containing milrinone. Milrinone-Claris should not be diluted in sodium bicarbonate intravenous solution.

4.6 Fertility, pregnancy and lactation
Pregnancy
Category B3
Oral administration of milrinone to pregnant rats and rabbits during organogenesis produced no evidence of teratogenicity at dose levels up to 40 mg/kg/day and 12 mg/kg/day respectively. 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 increased resorption rate was apparent at dose levels above 3 mg/kg/day (intravenous) in the latter species. There are no adequate and well-controlled studies in pregnant women. Milrinone-Claris should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

Fertility
No data available.

4.7 Effects on ability to drive and use machines
Ondansetron-Claris is unlikely to have any effect on a person’s ability to drive or operate machinery.
4.8 Undesirable effects
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://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

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.

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.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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.

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:

<table>
<thead>
<tr>
<th>Cardiac Index</th>
<th>Loading Injection (µg/kg)</th>
<th>Maintenance Infusion (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>37.5</td>
<td>0.375</td>
</tr>
<tr>
<td>38</td>
<td>50</td>
<td>0.500</td>
</tr>
<tr>
<td>42</td>
<td>75</td>
<td>0.750</td>
</tr>
</tbody>
</table>

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 0.50 µg/kg/min are approximately 200 ng/mL. Near maximal favourable 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.

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.

5.2 Pharmacokinetic properties

Following intravenous loading, injections of 12.5 to 125.0 µg/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 0.70 µg/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.

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 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

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

Carcinogenicity

Twenty-four months of oral administration of milrinone to mice at doses up to 40 mg/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 5 mg/kg/day for 24 months or at 25 mg/kg/day for up to 18 months in males and 20 months in females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Glucose, lactic acid, sodium hydroxide and water for injections.

6.2 Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life
24 months from date of manufacture.

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

6.6 Special precautions for disposal
No special requirements.

6.7 Physicochemical Properties
The chemical name is 1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile lactate.

![](image)

The CAS number is 78415-72-2 (milrinone), 100286-97-3 (milrinone lactate)
The empirical formula is C_{12}H_{9}N_{3}O (milrinone), C_{12}H_{9}N_{3}O.(C_{3}H_{6}O_{3})x (milrinone lactate) The molecular weight is 211.2 (milrinone), 301.3 (milrinone lactate). Milrinone is an off-white to tan crystalline powder.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

Milrinone-Claris is distributed in New Zealand by:
Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
NEW ZEALAND DATA SHEET

Auckland 1060
Phone: (09) 574 2400

9 DATE OF FIRST APPROVAL
12/11/2015

10 DATE OF REVISION OF THE TEXT
13/03/2018

SUMMARY TABLE OF CHANGES
Update to Sponsor details.