Alert	May cause hypotension. Caution advised when using loading dose. Reduce infusion rate in infants with renal impairment and prematurity.
Indication	Inotrope and vasodilator for: • Treatment of low cardiac output states and as an adjunct to inhaled nitric oxide in neonates with persistent pulmonary hypertension of the neonate [1]. • Prevention of low cardiac output syndrome (LCOS) post cardiac surgery[2, 3]. • Treatment of myocardial dysfunction in neonates and children with shock particularly in context of enteroviral 71 infection [4].
Action	Selective inhibitor of type 3 cAMP phosphodiesterase in cardiac and vascular muscle.
Drug Type	Inotrope and vasodilator.
Trade Name	Primacor, Milrinone GH.
Presentation	1 mg/mL (1000 microgram/mL) vial.
Dosage/Interval	**Term infants** Continuous IV infusion: 0.5 microgram/kg/minute (Range 0.33 - 0.75 microgram/kg/minute). OPTIONAL: Loading dose: 75 microgram/kg over 60 minutes (Caution - risk of hypotension with loading dose). **Pre-term infants** Continuous IV infusion: 0.2 microgram/kg/minute. OPTIONAL: Loading dose: 135 microgram/kg over 3 hours (Caution - risk of hypotension with loading dose). **Renal Impairment (including hypoplastic left heart syndrome undergoing surgery)** Continuous IV infusion: 0.2 -0.33 microgram/kg/minute.
Route	Continuous IV infusion.
Maximum Daily Dose	Maximum IV Infusion rate: 1 microgram/kg/minute – caution as risk of drug accumulation over time.
Preparation/Dilution	**<u>Term infants</u>** Draw up 1.5 mL/kg (1500 microgram/kg of milrinone) and make up to a final volume of 50 mL with sodium chloride 0.9%. **Infusing at a rate of 1 mL/hour = 0.5 microgram/kg/minute** OPTIONAL- Give a loading dose of 2.5 mL (75 microgram/kg) over 1 hour (Note: risk of hypotension with loading dose). **<u>Pre-term infants</u>** Draw up 1.5 mL/kg (1500 microgram/kg of milrinone) and make up to a final volume of 50 mL with sodium chloride 0.9%. **Infusing at a rate of 0.4 mL/hour = 0.2 microgram/kg/minute** OPTIONAL - Give a loading dose of 4.5 mL (135 microgram/kg) over 3 hours (Note: risk of hypotension with loading dose).
Administration	Continuous IV infusion preferably via a central line. Adjust infusion rate based on haemodynamic and clinical response. For term infants – if loading is not given, higher maintenance infusion may be required to reach the steady state – range 0.5-0.75 microgram/kg/minute. For preterm infants – if loading dose is not given, titrate the maximal infusion rate to 0.5 microgram/kg/minute if required. Avoid prolonged infusion > 0.2 microgram/kg/min in very preterm infants.

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Monitoring	Continuous heart rate, ECG and blood pressure monitoring preferable. Assess urine output and peripheral perfusion frequently. Monitor fluid and electrolytes.
Contraindications	Severe obstructive aortic or pulmonary valvular disease or hypertrophic subaortic stenosis. Hypersensitivity to milrinone, other 3,4'-bipyridines (inamrinone) or any other ingredient of the formulation.
Precautions	Ensure adequate circulating blood volume prior to commencement. **Loading dose:** Considered optional depending on clinical circumstances. May cause hypotension. Monitor BP and heart rate closely and ensure adequate volume replacement. **Prematurity:** Long half-life reported (10 hours) in very preterm infants.[5] Avoid prolonged higher rate infusion (≥0.2 microgram/kg/min). **Renal impairment:** Significantly increases half-life of milrinone. A reduction in the infusion rate in patients with renal impairment to prevent drug accumulation is advised. **Patient recovery:** 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.
Drug Interactions	None known.
Adverse Reactions	Ventricular arrhythmias in cardiac patients. Patent ductus arteriosus has been reported. May cause hypotension.
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9%. Y-site: Amino acid solutions, adrenaline (epinephrine) hydrochloride, amiodarone, atracurium, bivalirudin, calcium gluconate monohydrate, caspofungin, dexmedetomidine, digoxin, dobutamine, dopamine, doripenem, fentanyl, glyceryl trinitrate, heparin sodium, insulin (short-acting), magnesium sulfate heptahydrate, metoprolol, midazolam, morphine sulfate pentahydrate, noradrenaline (norepinephrine), pancuronium, potassium chloride, ranitidine, rocuronium, sodium nitroprusside, vecuronium, verapamil.
Incompatibility	Fluids: Sodium bicarbonate. Y-site: Bumetanide, esmolol, furosemide (frusemide), imipenem + cilastatin, ondansetron.
Stability	Diluted solution: Store below 30°C and use within 24 hours.
Storage	Vials: Store below 25°C.Protect from light. Discard remainder after use.
Special Comments	Discard admixtures exhibiting colour change.
Evidence summary	Efficacy: Treatment of pulmonary hypertension in near term infants: Case series report improvements in pulmonary and systemic haemodynamics and oxygenation in infants with pulmonary hypertension treated with nitric oxide. [1, 6, 7] (LOE IV GOR C) Treatment of very pre-term infants: An RCT found no difference in measures of systemic blood flow when used preventatively in extremely premature infants. [8] Case series reported improvement in oxygenation and a fall in blood pressure in pre-term infants with pulmonary hypertension treated with nitric oxide. [9] There are insufficient data to determine the efficacy and safety of milrinone in pre-term infants with pulmonary hypertension and/or myocardial dysfunction.[10] (LOE II [8], GOR C) Neonates and infants undergoing cardiac surgery: A single RCT found high dose milrinone reduced the risk of LCOS post cardiac surgery. [2, 3] (LOE II, GOR B) An historical control study reported use of milrinone post ductal ligation improved ventilation and reduced inotrope use [11] (LOE IV, GOR C). Infants and children with shock associated with myocardial dysfunction: An RCT found milrinone 0.5 microgram/kg/min reduced mortality in children with enterovirus 71-induced pulmonary

	oedema and/or shock. A loading dose was not used. [4] (LOE II, GOR B) Safety: Reports of arrhythmias, tachycardia, hypotension and hypokalaemia, bronchospasm, headaches, thrombocytopenia, anaemia and elevated serum liver enzymes. In neonates treated with milrinone, hypotension and intraventricular haemorrhage have been observed. [2, 6] (LOE IV) Pharmacokinetics: Extremely pre-term infants for prevention of low systemic blood flow: $T_{½}$ averaged 10 hours. Milrinone loading infusion 0.75 microgram/kg/min for 3 hours followed by maintenance infusion 0.2 microgram/kg/min achieved target (180–300 nanogram/mL).[5] (LOE IV GOR C) Term infants with pulmonary hypertension: Half-life ($t_{½}$) averaged 4 hours. Loading dose 50 microgram/kg resulted in sub-therapeutic concentrations. Maintenance infusion 0.33–0.99 microgram/kg/min resulted in concentrations above target range (180–300 nanogram/mL).[1] (LOE IV GOR C) Term newborns with hypoplastic left heart undergoing surgery: Neonates received an initial dose of either a 100 or 250 microgram/kg of milrinone into the cardiopulmonary bypass circuit. A constant infusion of 0.5 microgram/kg/min resulted in drug accumulation during the initial 12 h of drug administration. Postoperatively, milrinone clearance was significantly impaired. Initial loading dose of 100 microgram/kg on CPB resulted in plasma concentrations similar to those observed in other therapeutic settings. In the postoperative setting of markedly impaired renal function, an infusion rate of 0.2 microgram/kg/min should be considered.[12] Paediatric patients with septic shock: $T_{½}$ averaged 1.47 hours (range, 0.62 to 10.85 hours). Loading dose 75 microgram/kg and starting infusion rates 0.75–1.0 microgram/kg/min for patients with normal renal function recommended.[13] Prevention of low cardiac output syndrome post cardiac surgery in infants: Loading dose 50 microgram/kg then infusion 3 microgram/kg/min for 30 minutes and then a maintenance infusion 0.5 microgram/kg/min, with adjustment for age.[14] (LOE IV GOR C).
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