Milrinone
Newborn use only

2021

<table>
<tr><td>Alert</td><td>May cause hypotension. Caution advised when using loading dose.
Reduce infusion rate for infants with renal impairment and prematurity.</td></tr>
<tr><td>Indication</td><td>Inotrope and vasodilator for:
1. Treatment of low cardiac output and as an adjunct to inhaled nitric oxide in neonates with persistent pulmonary hypertension of the neonate [1].
2. Prevention of low cardiac output syndrome (LCOS) post cardiac surgery[2, 3].
3. Treatment of myocardial dysfunction in neonates and children with shock particularly in context of enteroviral 71 infection [4].</td></tr>
<tr><td>Action</td><td>Selective inhibitor of type 3 cAMP phosphodiesterase in cardiac and vascular muscle.</td></tr>
<tr><td>Drug type</td><td>Inotrope and vasodilator.</td></tr>
<tr><td>Trade name</td><td>Primacor, Milrinone GH, Milrinone-Baxter</td></tr>
<tr><td>Presentation</td><td>10mg/10mL (1000 microgram/mL) vial.</td></tr>
<tr><td>Dose</td><td>STANDARD Regimen – with NO loading dose
<table>
<tr><th></th><th>Term infant</th><th>Preterm infant</th></tr>
<tr><td>Maintenance NO loading dose</td><td>0.33 − 0.75 microgram/kg/minute</td><td>0.2 microgram/kg/minute</td></tr>
</table>
OPTIONAL Regimen – with loading dose
Caution: Risk of hypotension with loading dose!
<table>
<tr><th></th><th>Term infant</th><th>Preterm infant</th></tr>
<tr><td rowspan="2">OPTIONAL Loading dose Followed by maintenance dose</td><td>Loading: 75 microgram/kg over 1 hour</td><td>Loading: 45 microgram/kg over 1 hour</td></tr>
<tr><td>0.33 − 0.75 microgram/kg/minute</td><td>0.2 microgram/kg/minute</td></tr>
</table></td></tr>
<tr><td>Dose adjustment</td><td>Renal impairment (including hypoplastic left heart syndrome undergoing surgery)
0.2 −0.33 microgram/kg/minute IV infusion</td></tr>
<tr><td>Maximum dose</td><td>Maximum IV Infusion rate for the maintenance dose is 1 microgram/kg/minute and 0.5 microgram/kg/minute for term and preterm infants respectively – caution as risk of drug accumulation over time.</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV infusion.</td></tr>
<tr><td>Preparation</td><td><u>Term infant</u>
<u>Standard Regimen – with NO loading dose</u>
<table>
<tr><th><u>Infusion strength</u></th><th><u>Prescribed amount</u></th></tr>
<tr><td>1 mL/hour = 0.33 microgram/kg/minute</td><td>1 mL/kg milrinone and make up to 50mL</td></tr>
</table>
Draw up 1mL/kg (1000 microgram/kg of milrinone) and add sodium chloride 0.9% or glucose 5% to make a final volume of 50mL. Infusing at a rate of 1mL/hour = 0.33 microgram/kg/minute.

For term infants – if loading is not given, higher maintenance infusion may be required to reach the steady drug range of 0.5−0.75 microgram/kg/minute.

<u>Preterm infant and renal impairment</u>
<u>Standard Regimen – with NO loading dose</u>
<table>
<tr><th><u>Infusion strength</u></th><th><u>Prescribed amount</u></th></tr>
<tr><td>1 mL/hour = 0.2 microgram/kg/minute</td><td>0.6 mL/kg milrinone and make up to 50mL</td></tr>
</table>
Draw up 0.6mL/kg (600 microgram/kg of milrinone) and add sodium chloride 0.9% or glucose 5% to make a final volume of 50mL. Infusing 1mL/hour = 0.2microgram/kg/minute.</td></tr>
</table>

	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/minute in very preterm infants. **Term infant** **Optional Regimen – with loading dose** Give a loading dose of 3.75 mL (75 microgram/kg) over 1 hour (Note: risk of hypotension with loading dose). **Preterm infant** **Optional Regimen – with loading dose** Give a loading dose of 3.75 mL (45 microgram/kg) over 1 hour (Note: risk of hypotension with loading dose).
Administration	Continuous IV infusion preferably via central line. Change solution every 24 hours. Adjust infusion rate based on haemodynamic and clinical response. For Loading dose: IV infusion over ONE hour
Monitoring	Heart rate, ECG and blood pressure Urine output and peripheral perfusion frequently. Fluid and electrolytes. Liver function. Platelets
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/minute. **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. May cause hypotension.
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9%. Y-site: Amino acid solutions, aciclovir, adrenaline (epinephrine) hydrochloride, amikacin, amiodarone, atracurium, bivalirudin, calcium chloride, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, dexmedetomidine, digoxin, dobutamine, dopamine, doripenem, fentanyl, glyceryl trinitrate, heparin sodium, insulin (short-acting), magnesium sulfate heptahydrate, meropenem, metoprolol, midazolam, morphine sulfate pentahydrate, noradrenaline (norepinephrine), pancuronium, potassium chloride, ranitidine, rocuronium, sodium nitroprusside, vancomycin, vecuronium, verapamil.
Incompatibility	Fluids: Sodium bicarbonate. Y-site: Bumetanide, esmolol, furosemide (frusemide), imipenem + cilastatin, ondansetron.
Stability	Primacore: If storage is necessary, diluted solution may be stored below 30°C and use within 24 hours. Milrinone GH: If storage is necessary, diluted solution may be stored at 2-8°C and use within 24 hours.

	Milrinone-Baxter: Diluted solution should be used immediately or as soon as practical to reduce microbiological hazard.
Storage	Primacor and Milrinone Baxter: Store below 30°C. Do not freeze. Milrinone GH: Store below 25°C. Do not freeze. Protect from light.
Excipients	Primacore, Milrinone GH, Milrinone-Baxter: Glucose (monohydrate or anhydrous), lactic acid or sodium hydroxide (for pH adjustment), and water for injections.
Special comments	Discard mixtures exhibiting colour change.
Evidence	**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: T½ 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 cardiopulmonary bypass 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: T½ 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).
Practice points	
References	1. McNamara PJ, Shivananda SP, Sahni M, Freeman D, Taddio A. Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2013;14:74-84.

2. Burkhardt BE, Rucker G, Stiller B. Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. The Cochrane database of systematic reviews. 2015;3:CD009515.
3. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, Bailey JM, Akbary A, Kocsis JF, Kaczmarek R, Spray TL, Wessel DL. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107:996-1002.
4. Chi CY, Khanh TH, Thoa le PK, Tseng FC, Wang SM, Thinh le Q, Lin CC, Wu HC, Wang JR, Hung NT, Thuong TC, Chang CM, Su IJ, Liu CC. Milrinone therapy for enterovirus 71-induced pulmonary edema and/or neurogenic shock in children: a randomized controlled trial. Critical care medicine. 2013;41:1754-60.
5. Paradisis M, Jiang X, McLachlan AJ, Evans N, Kluckow M, Osborn D. Population pharmacokinetics and dosing regimen design of milrinone in preterm infants. Archives of disease in childhood Fetal and neonatal edition. 2007;92:F204-9.
6. James AT, Corcoran JD, McNamara PJ, Franklin O, El-Khuffash AF. The effect of milrinone on right and left ventricular function when used as a rescue therapy for term infants with pulmonary hypertension. Cardiology in the young. 2015:1-10.
7. McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. Journal of critical care. 2006;21:217-22.
8. Paradisis M, Evans N, Kluckow M, Osborn D. Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. The Journal of pediatrics. 2009;154:189-95.
9. James AT, Bee C, Corcoran JD, McNamara PJ, Franklin O, El-Khuffash AF. Treatment of premature infants with pulmonary hypertension and right ventricular dysfunction with milrinone: a case series. Journal of perinatology : official journal of the California Perinatal Association. 2015;35:268-73.
10. Bassler D, Kreutzer K, McNamara P, Kirpalani H. Milrinone for persistent pulmonary hypertension of the newborn. The Cochrane database of systematic reviews. 2010:CD007802.
11. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. The Journal of pediatrics. 2012;160:584-9 e1.
12. Zuppa AF, Nicolson SC, Adamson PC, Wernovsky G, Mondick JT, Burnham N, Hoffman TM, Gaynor JW, Davis LA, Greeley WJ, Spray TL, Barrett JS. Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. Anesthesia and analgesia. 2006;102:1062-9.
13. Lindsay CA, Barton P, Lawless S, Kitchen L, Zorka A, Garcia J, Kouatli A, Giroir B. Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. The Journal of pediatrics. 1998;132:329-34.
14. Bailey JM, Miller BE, Lu W, Tosone SR, Kanter KR, Tam VK. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology. 1999;90:1012-8.
15. MIMS accessed via CIAP on 4th November 2015
16. Australian Injectable Drugs Handbook, 6th Edition, Society of Hospital Pharmacists of Australia 2015.
17. Micromedex 2.0 accessed via CIAP on 4th November 2015

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