respectively after 6 weeks. This represented a milk to serum ratio of 2.0 and 1.1 respectively. However, mexiletine was undetectable in the infant's serum on both occasions and no adverse effects were seen. In another report[2] a woman taking a similar dose of mexiletine for the last 5 months of her pregnancy also breast fed her infant. In samples of maternal milk and blood collected between the second and fifth day postpartum the milk to plasma ratio varied between 0.78 and 1.89 with a mean of 1.45. It was considered unlikely that the infant would ingest more than 1.25 mg of mexiletine in any 24-hour period, and this amount was not thought to be enough to cause adverse effects. Failure to feed was noted[3] in the first 17 days in an infant whose mother was taking 750 mg daily of mexiletine and 50 mg daily of atenolol. After maternal education and formula supplementation an acceptable growth curve was established. Breast feeding continued until the infant was 3 months old, and no adverse effects were seen at 10 months. The American Academy of Pediatrics[4] therefore considers that mexiletine is usually compatible with breast feeding.


1. Timmis AD, *et al*. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lewis AM, *et al.* Mexiletine in human blood and breast milk. *Postgrad Med J* 1981; **57:** 546–7.
3. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)


**Pregnancy.** Mexiletine crosses the placenta but there have been several reports of its use in pregnant women with no apparent long-term effects on the infants. A normal infant was born to a woman given mexiletine with propranolol for the control of ventricular tachycardia during the third trimester of pregnancy.[1] During the first 6 hours after delivery the infant had a heart rate of only 90 beats/minute, probably due to the propranolol; it was normal thereafter. At delivery the serum concentration of mexiletine in mother and infant was the same. A woman[2] who received mexiletine and atenolol throughout pregnancy also delivered a normal infant; failure to feed was noted at 17 days but at 10 months no adverse effects were seen. In another case[3] where the mother took mexiletine throughout pregnancy, the infant had a low Apgar score at 1 minute and hypoglycaemia was also noted, but the relationship to mexiletine was unclear; cord and maternal blood concentrations at the time of delivery were 400 nanograms/mL and 600 nanograms/mL, respectively.


1. Timmis AD, *et al*. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
3. Gregg AR, Tomich PG. Mexilitene [sic] use in pregnancy. *J Perinatol* 1988; **8:** 33–5.


## Interactions

Mexiletine undergoes extensive metabolism in the liver particularly by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6, and possibly CYP3A4, and interactions may occur with other drugs metabolised by the same enzymes. Plasma concentrations of mexiletine may be reduced by hepatic enzyme inducers such as phenytoin and rifampicin; increased plasma concentrations may occur with enzyme inhibitors.

Absorption of mexiletine may be delayed by drugs that slow gastric emptying such as opioid analgesics and atropine. The rate of absorption may be increased by metoclopramide; the extent of absorption is unaffected.

Drugs that acidify or alkalinise the urine enhance or reduce the rate of elimination of mexiletine, respectively.

There may be an increased risk of arrhythmias if mexiletine is used with other antiarrhythmics or with arrhythmogenic drugs.

Mexiletine has been reported to increase theophylline concentrations (p.1142) and to precipitate lidocaine toxicity (p.1863).

## Pharmacokinetics

Mexiletine is readily and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 90%, although absorption may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Mexiletine is metabolised in the liver to a number of metabolites; metabolism may involve cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, and genetic polymorphism in relation to CYP2D6 has been identified. Mexiletine is excreted in the urine, mainly in the form of its metabolites with about 10% excreted unchanged; clearance is increased in acid urine.

Mexiletine is widely distributed throughout the body and is about 50 to 70% bound to plasma proteins. Mexiletine crosses the placenta and is distributed into breast milk. It has an elimination half-life of about 10 hours in healthy subjects but this may be prolonged in patients with heart disease, hepatic impairment, or severe renal impairment. Its therapeutic effect has been correlated with plasma concentrations of 0.5 to 2 micrograms/mL, but the margin between therapeutic and toxic concentrations is narrow, and severe toxicity may occur within this range.

◊ References.


1. Labbé L, Turgeon J. Clinical pharmacokinetics of mexiletine. *Clin Pharmacokinet* 1999; **37:** 361–84.


## Uses and Administration

Mexiletine is a class Ib antiarrhythmic (p.1153) with actions similar to those of lidocaine (p.1864), to which it is structurally related. Unlike lidocaine it undergoes little hepatic first-pass metabolism and can be given orally.

Mexiletine is used for the treatment of ventricular **arrhythmias** (p.1160). It is given orally or intravenously as the hydrochloride.

Mexiletine hydrochloride is given orally in a usual loading dose of 400 mg followed by 200 to 250 mg three or four times daily, starting 2 hours after the loading dose. The usual maintenance dosage is 600 to 900 mg daily in divided doses; doses up to 1.2 g daily may be given. Oral doses should be taken with food and swallowed with plenty of liquid to avoid oesophageal ulceration. Modified-release preparations have been used. Higher loading doses (for example, of 600 mg) may be necessary in patients after myocardial infarction to overcome delayed absorption, especially if they have received an opioid analgesic.

Mexiletine hydrochloride may be given by slow intravenous injection in doses of 100 to 250 mg at a rate of 25 mg/minute, followed by an infusion at a rate of 250 mg over 1 hour, 250 mg over the next 2 hours, and then at about 500 micrograms/minute for maintenance, according to response; when appropriate the patient may be transferred to oral therapy with doses of 200 to 250 mg three or four times daily. Alternatively, an initial intravenous dose of 200 mg at a rate of 25 mg/minute, may be followed by an oral dose of 400 mg on completion of the injection, with subsequent oral therapy as above.

Mexiletine has also been tried in the treatment of refractory neuropathic **pain** (see below).

**Administration in children.** Mexiletine may be effective for ventricular arrhythmias in children; a study[1] of 42 children and young adults (age range 5 months to 34 years) found that mexiletine, given orally in a dose of 1.4 to 5 mg/kg every 8 hours, was effective in 30 patients (71%), with long-term control reported in 18. Treatment was more effective in children with congenital heart disease than in those with cardiomyopathy or no heart disease. Another report[2] found that young children required higher mg/kg doses than adults; a 2-week-old girl and a 20-month-old boy required oral doses of 25 and 15 mg/kg daily, respectively, to produce therapeutic plasma concentrations and control of tachycardia.


1. Moak JP, *et al*. Mexiletine: an effective antiarrhythmic drug for treatment of ventricular arrhythmias in congenital heart disease. *J Am Coll Cardiol* 1987; **10:** 824–9.
2. Holt DW, *et al*. Paediatric use of mexiletine and disopyramide. *BMJ* 1979; **2:** 1476–7.


**Administration in the elderly.** The rate of absorption of mexiletine was slower in a group of 7 elderly subjects compared with 8 young subjects given mexiletine 100 mg by mouth, but the extent of absorption was probably not affected.[1] Elimination of mexiletine was not significantly different between the 2 groups and there was no pharmacokinetic basis for dosage modification of mexiletine in the elderly. An observational study[2] in patients receiving mexiletine found a small decrease in clearance with age, but again this was not considered to warrant dosage adjustment.


1. Grech-Bélanger O, *et al*. Pharmacokinetics of mexiletine in the elderly. *J Clin Pharmacol* 1989; **29:** 311–15.
2. Ueno K, *et al*. Pharmacokinetics of mexiletine in middle-aged and elderly patients. *Clin Pharm* 1993; **12:** 768–70.


**Administration in renal impairment.** The pharmacokinetics of mexiletine do not appear to be affected by renal impairment,[1] although one study[2] found that in patients with creatinine clearance below 10 mL/minute the steady-state plasma concentration and half-life were increased, suggesting that dosage should be adjusted according to plasma concentrations in such patients. Haemodialysis[1] and continuous ambulatory peritoneal dialysis[3] do not appear to affect mexiletine clearance.


1. Wang T, *et al*. Pharmacokinetics and nondialyzability of mexiletine in renal failure. *Clin Pharmacol Ther* 1985; **37:** 649–53.
2. El Allaf D, *et al.* Pharmacokinetics of mexiletine in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 431–5.
3. Guay DRP, *et al*. Mexiletine clearance during peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 857–8.


**Pain.** Neuropathic pain (p.8) is often insensitive to opioid analgesics and various drugs, including mexiletine, have been tried. Mexiletine may be of benefit in diabetic neuropathy,[1] although studies have given conflicting results; two of the studies that reported no difference between treatment and placebo found that a subset of patients (those with stabbing or burning pain, heat sensations, and formication) appeared to benefit.[2,3] There have also been reports of improvement in patients with central post-stroke pain (thalamic pain syndrome),[4] and in neuropathic pain associated with cancer,[5-7] and a systematic review[8] concluded that mexiletine was safe and effective in various types of neuropathic pain.

Other painful states in which mexiletine has been reported to be of benefit include: Dercum's disease (a condition involving painful fatty deposits),[9] and erythromelalgia.[10,11]


1. Jarvis B, Coukell AJ. Mexiletine: a review of its therapeutic use in painful diabetic neuropathy. *Drugs* 1998; **56:** 691–707.
2. Stracke H, *et al*. Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992; **15:** 1550–5.
3. Wright JM, *et al.* Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997; **31:** 29–34.
4. Awerbuch GI, Sandyk R. Mexiletine for thalamic pain syndrome. *Int J Neurosci* 1990; **55:** 129–33.
5. Colclough G, *et al.* Mexiletine for chronic pain. *Lancet* 1993; **342:** 1484–5.
6. Sloan P, *et al.* Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. *Anesth Analg* 1999; **89:** 760–1.
7. Fassoulaki A, *et al.* The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* 2002; **95:** 985–91.
8. Challapalli V, *et al.* Systemic administration of local anesthetic agents to relieve neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/07).
9. Petersen P, *et al*. Treating the pain of Dercum's disease. *BMJ* 1984; **288:** 1880.
10. Nathan A, *et al.* Primary erythromelalgia in a child responding to intravenous lidocaine and oral mexiletine treatment. Abstract: *Pediatrics* 2005; **115:** 1066. Full version: http://pediatrics.aappublications.org/cgi/content/full/115/4/e504 (accessed 10/07/07)
11. Kuhnert SM, *et al*. Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999; **135:** 1447–9.


## Preparations

***BP 2008:*** Mexiletine Capsules; Mexiletine Injection;
***USP 31:*** Mexiletine Hydrochloride Capsules.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Mexitilen; ***Austral.:*** Mexitil; ***Austria:*** Mexitil; ***Belg.:*** Mexitil; ***Braz.:*** Mexitil; ***Canad.:*** Mexitil†; ***Cz.:*** Katen; ***Fin.:*** Mexitil; ***Fr.:*** Mexitil†; ***Ger.:*** Mexitil; ***Gr.:*** Mexitil; Myovek†; ***Hong Kong:*** Mexitil†; ***Hung.:*** Ritalmex; ***India:*** Mexitil; ***Irl.:*** Mexitil; ***Israel:*** Mexilen; ***Ital.:*** Mexitil; ***Jpn:*** Mexitil; ***Mex.:*** Mexitil†; ***Neth.:*** Mexitil†; ***NZ:*** Mexitil; ***Pol.:*** Mexicord; ***S.Afr.:*** Mexitil†; ***Spain:*** Mexitil; ***Swed.:*** Mexitil†; ***Thai.:*** Mexitil†; ***Turk.:*** Mexitil; ***UK:*** Mexitil†; ***USA:*** Mexitil; ***Venez.:*** Tumetil.

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## Mibefradil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mibefradil; Mibéfradil, Chlorhydrate de; Mibefradil Dihydrochloride *(USAN)*; Mibefradili Hydrochloridum; Ro-40-5967 (mibefradil); Ro-40-5967/001 (mibefradil hydrochloride). (1*S*,2*S*)-(2-{[3-(2-Benzimidazolyl)propyl]methylamino}-ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride.

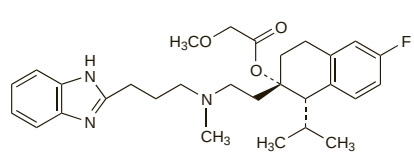
Мибефрадила Гидрохлорид

$C_{29}H_{38}FN_3O_3,2HCl$ = 568.6.

*CAS — 116644-53-2 (mibefradil); 116666-63-8 (mibefradil hydrochloride).*

*ATC — C08CX01.*

*ATC Vet — QC08CX01.*



*(mibefradil)*

### Profile

Mibefradil is a calcium-channel blocker that acts principally on fast T-type calcium channels, unlike conventional calcium-channel blockers that act on slow L-type channels (see p.1154). Mibe-

fradil was introduced for the management of hypertension and angina pectoris but was withdrawn worldwide several months later due to increasing reports of serious interactions with a wide range of drugs.

## Midodrine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de midodrina; Midodrine, Chlorhydrate de; Midodrini Hydrochloridum; ST-1085 (midodrine or midodrine hydrochloride). 2-Amino-*N*-(β-hydroxy-2,5-dimethoxyphenethyl)-acetamide hydrochloride; (*RS*)-*N*$^1$-(β-Hydroxy-2,5-dimethoxyphenethyl)glycinamide hydrochloride.

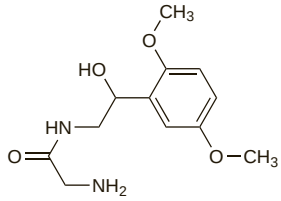
Мидодрина Гидрохлорид

$C_{12}H_{18}N_2O_4$,HCl = 290.7.

*CAS — 42794-76-3 (midodrine); 3092-17-9 (midodrine hydrochloride).*

*ATC — C01CA17.*

*ATC Vet — QC01CA17.*



*(midodrine)*

### Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p.1407. Midodrine has mainly alpha-agonist properties and the most serious adverse effect of midodrine is supine hypertension. Paraesthesias, dysuria, pilomotor reaction (goose flesh), pruritus and rashes have been reported.

### Interactions

As for Sympathomimetics, p.1407.

### Pharmacokinetics

Midodrine is well absorbed from the gastrointestinal tract and undergoes enzymatic hydrolysis in the systemic circulation to its active metabolite, deglymidodrine (desglymidodrine; ST-1059). Midodrine itself reaches its peak plasma concentrations about half an hour after an oral dose, and has a plasma half-life of about 25 minutes. The active metabolite reaches its peak plasma concentration about an hour after oral dosage and has a terminal elimination half-life of about 3 hours. Deglymidodrine undergoes some further metabolism in the liver. Midodrine is primarily excreted in the urine as metabolites and a small amount of unchanged drug.

### Uses and Administration

Midodrine is a direct-acting sympathomimetic (p.1408) with selective alpha-agonist activity; the main active moiety has been stated to be its major metabolite, deglymidodrine. It acts as a peripheral vasoconstrictor but has no direct cardiac stimulatory effects.

Midodrine hydrochloride is used in the treatment of hypotensive states (p.1174) and in particular of orthostatic hypotension (p.1530). Alpha-agonist drugs such as midodrine have also been used as an adjunct in the management of urinary incontinence (p.2180).

In **hypotensive states**, the usual initial oral dose of midodrine hydrochloride is 2.5 mg two or three times daily, adjusted gradually according to response; up to 10 mg three times daily may be required. The potential for supine hypertension is reduced by taking the last dose of the day at least 4 hours before bedtime.

An oral dose for **urinary incontinence** is 2.5 to 5 mg two or three times daily.

Midodrine hydrochloride can also be given in similar doses by slow intravenous injection. It has also been used orally or by injection in the treatment of **retrograde ejaculation**.

◊ References.


1. McClellan KJ, *et al.* Midodrine: a review of its therapeutic use in the management of orthostatic hypotension. *Drugs Aging* 1998; **12:** 76–86.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; **19:** 2553–8.


### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Austria:*** Gutron; ***Canad.:*** Amatine; ***Chile:*** Gutron; ***Cz.:*** Gutron; ***Fr.:*** Gutron; ***Ger.:*** Gutron; ***Hong Kong:*** Gutron; ***Hung.:*** Gutron; ***Irl.:*** Midon; ***Israel:*** Gutron; ***Ital.:*** Gutron; Xerotil; ***Jpn:*** Metligine; ***Neth.:*** Gutron; ***NZ:*** Gutron; ***Pol.:*** Gutron; ***Port.:*** Gutron; ***Rus.:*** Gutron (Гутрон); ***Singapore:*** Gutron; ***Switz.:*** Gutron; ***Thai.:*** Gutron†; ***USA:*** ProAmatine.

## Milrinone *(BAN, USAN, rINN)*

Milrinona; Milrinonum; Win-47203-2. 1,6-Dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile.

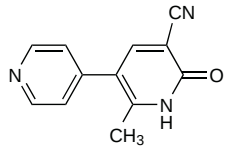
Мильринон

$C_{12}H_9N_3O$ = 211.2.

*CAS — 78415-72-2.*

*ATC — C01CE02.*

*ATC Vet — QC01CE02.*



**Pharmacopoeias.** In *US.*

**USP 31** (Milrinone). A white to tan, hygroscopic, crystalline solid. Practically insoluble in water and in chloroform; very slightly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers.

## Milrinone Lactate *(BANM, rINNM)*

Lactato de milrinona; Milrinone, Lactate de; Milrinoni Lactas.

Мильринона Лактат

$C_{12}H_9N_3O$,$C_3H_6O_3$ = 301.3.

*ATC — C01CE02.*

*ATC Vet — QC01CE02.*

**Incompatibility.** UK licensed product information states that milrinone lactate injection is incompatible with furosemide and bumetanide, and it should not be diluted with sodium bicarbonate injection. Physical incompatibility with imipenem-cilastatin sodium has also been reported.[1]


1. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health-Syst Pharm* 2002; **59:** 452–4.


### Adverse Effects and Precautions

Prolonged oral use of milrinone has increased the mortality rate and milrinone is now only used intravenously for short-term use.

Supraventricular and ventricular arrhythmias, hypotension, angina-like chest pain, and headache have been reported. Hypokalaemia, tremor, and thrombocytopenia may occur. The incidence of arrhythmias may be lower in *children* whereas the risk of thrombocytopenia may be higher (see Administration in Children, below).

Milrinone should be used with caution in patients with severe obstructive aortic or pulmonary valvular disease or with hypertrophic cardiomyopathy. Since milrinone may facilitate conduction through the atrioventricular node it can increase the ventricular response rate in patients with atrial flutter or fibrillation. Digitalisation should be considered in these patients before milrinone therapy is started.

Blood pressure, heart rate, ECG, fluid and electrolyte balance, and renal function should be monitored during milrinone therapy.

Milrinone should be given in reduced doses to patients with renal impairment.

### Pharmacokinetics

Although milrinone is rapidly and almost completely absorbed from the gastrointestinal tract, it is only given intravenously. It is about 70% bound to plasma proteins. Elimination occurs mainly via the urine; about 83% of a dose is excreted as unchanged drug. The elimination half-life is about 2.3 hours.

◊ General references.


1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).


### Uses and Administration

Milrinone is a phosphodiesterase inhibitor similar to amrinone (p.1215) with positive inotropic and vasodilator activity. It is, however, reported to have greater positive inotropic activity than amrinone. It is given intravenously, as the lactate, in the short-term management of severe heart failure unresponsive to other forms of therapy and in acute heart failure after cardiac surgery. In some longer-term studies milrinone was given by mouth, but an increased mortality rate was reported.

Doses of milrinone lactate are expressed in terms of the base; milrinone lactate 1.43 mg is equivalent to about 1 mg of milrinone. The initial loading dose is the equivalent of milrinone 50 micrograms/kg given over 10 minutes followed by a continuous maintenance infusion. The maintenance infusion may be titrated between 375 and 750 nanograms/kg per minute but a total daily dose of 1.13 mg/kg should not be exceeded.

Dosage should be reduced in patients with renal impairment (see below).

**Administration in children.** Milrinone has been used in children with septic shock or heart failure after cardiac surgery. Pharmacokinetic studies[1,2] have suggested that steady-state plasma concentrations of milrinone are lower in children than in adults given similar doses, and that milrinone clearance is faster in children. Higher doses in proportion to body-weight may therefore be necessary in children than in adults. For neonates and children aged 1 month to 18 years with heart failure, low cardiac output after cardiac surgery, or shock, the *BNFC* recommends an initial dose of 50 to 75 micrograms/kg by intravenous infusion over 30 to 60 minutes, followed by continuous intravenous infusion at a dose of 30 to 45 micrograms/kg per hour (500 to 750 nanograms/kg per minute). The infusion may be continued for 2 to 3 days, but is usually given for 12 hours after cardiac surgery.

Milrinone also appears to be effective for the prevention of low cardiac output in children undergoing cardiac surgery.[3] It has been tried for the prevention of low systemic blood flow in premature infants, but further studies are needed to confirm its role.[4]

A study[5] of adverse effects in children given milrinone has suggested that arrhythmias are less common than in adults whereas thrombocytopenia is more common.


1. Lindsay CA, *et al.* Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; **132:** 329–34.
2. Ramamoorthy C, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998; **86:** 283–9.
3. Hoffman TM, *et al.* 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. Paradisis M, *et al.* Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr* 2006; **148:** 306–13.
5. Watson S, *et al.* Use of milrinone in the pediatric critical care unit. *Pediatrics* 1999; **104** (suppl): 681–2.


**Administration in renal impairment.** Doses of milrinone should be reduced in patients with renal impairment. The following doses for maintenance infusion are recommended based on creatinine clearance (CC):

- CC 50 mL/minute: 430 nanograms/kg per minute
- CC 40 mL/minute: 380 nanograms/kg per minute
- CC 30 mL/minute: 330 nanograms/kg per minute
- CC 20 mL/minute: 280 nanograms/kg per minute
- CC 10 mL/minute: 230 nanograms/kg per minute
- CC 5 mL/minute: 200 nanograms/kg per minute

**Heart failure.** Milrinone is one of several drugs that may be used in heart failure (p.1165), but because of an increased mortality rate reported following long-term oral use it is usually only given intravenously for short-term management of heart failure unresponsive to other treatments. The PROMISE (Prospective Randomized Milrinone Survival Evaluation) study[1] showed that oral milrinone increased morbidity and mortality in patients with severe chronic heart failure. However, more recently, longer-term continuous intravenous use for up to 8 weeks has been studied in patients awaiting heart transplantation and appeared to be well tolerated.[2] Intermittent use on several days a week has also been tried.[3]

In patients with acute exacerbation of heart failure, a prospective study[4] found no benefit from the routine use of short-term intravenous milrinone.


1. Packer M, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; **325:** 1468–75.
2. Mehra MR, *et al.* Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; **80:** 61–4.
3. Cesario D, *et al.* Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. *Am Heart J* 1998; **135:** 121–9.
4. Cuffe MS, *et al.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287:** 1541–7.


### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Corotrope; ***Austral.:*** Primacor; ***Austria:*** Corotrop; ***Belg.:*** Corotrope; ***Braz.:*** Primacor; ***Canad.:*** Primacor†; ***Chile:*** Corotrope; ***Cz.:*** Corotrop; ***Fr.:*** Corotrope; ***Ger.:*** Corotrop; ***Gr.:*** Corotrope; ***Hong Kong:*** Primacor; ***Hung.:*** Corotrope; ***India:*** Milicor; ***Israel:*** Primacor; ***Jpn:*** Milrila;