fradil was introduced for the management of hypertension and angina pectoris but was withdrawn worldwide several months later due to increasing reports of serious interactions with a wide range of drugs.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

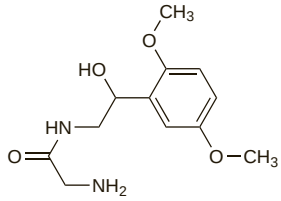
Мидодрина Гидрохлорид

$C_{12}H_{18}N_2O_4$,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.

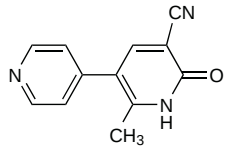
Мильринон

$C_{12}H_9N_3O$ = 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;