fradil was introduced for the management of hypertension and angina pectoris but was withdrawn worldwide several months later due to increasing reports of serious interactions with a wide range of drugs.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

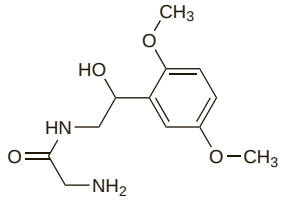
Мидодрина Гидрохлорид

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

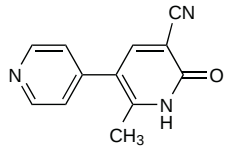
Мильринон

$C_{12}H_9N_3O$ = 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;

Malaysia: Primacor; ***Mex.:*** Primacor; ***Neth.:*** Corotrope; ***NZ:*** Primacor; ***Pol.:*** Corotrope; ***Port.:*** Corotrope; ***Singapore:*** Primacor; ***Spain:*** Corotrope; ***Swed.:*** Corotrop; ***Switz.:*** Corotrop; ***Thai.:*** Primacor; ***UK:*** Primacor; ***USA:*** Primacor; ***Venez.:*** Corotrope.

Minoxidil *(BAN, USAN, rINN)*

Minoksidiili; Minoksidilis; Minoxidilum; U-10858. 2,6-Diamino-4-piperidinopyrimidine 1-oxide.

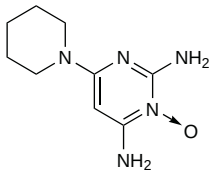
Миноксидил

$C_9H_{15}N_5O$ = 209.2.

CAS — 38304-91-5.

ATC — C02DC01; D11AX01.

ATC Vet — QC02DC01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Minoxidil). A white or almost white crystalline powder. Slightly soluble in water; soluble in methyl alcohol and in propylene glycol. Protect from light.

USP 31 (Minoxidil). A white or off-white crystalline powder. Slightly soluble in water; soluble in alcohol and in propylene glycol; practically insoluble in acetone, in chloroform, in ethyl acetate, and in petroleum spirit; sparingly soluble in methyl alcohol.

Adverse Effects and Treatment

Adverse effects commonly caused by minoxidil include reflex tachycardia, fluid retention accompanied by weight gain, oedema, and sometimes deterioration of existing heart failure and changes in the ECG. Hypertrichosis develops in up to 80% of patients within 3 to 6 weeks of the start of minoxidil therapy but is slowly reversible on discontinuation. Pericardial effusion, sometimes with associated tamponade, has been reported in about 3% of patients. Pericarditis may also occur. Minoxidil may aggravate or uncover angina pectoris. Other less frequent adverse effects include headache, nausea, gynaecomastia and breast tenderness, polymenorrhoea, allergic skin rashes, Stevens-Johnson syndrome, and thrombocytopenia.

Reflex tachycardia can be overcome by the use of a beta blocker, or alternatively methyldopa, and a diuretic (usually a loop diuretic) is used to reduce fluid retention. If excessive hypotension occurs, an intravenous infusion of sodium chloride 0.9% can be given to maintain the blood pressure. If a pressor agent is necessary, drugs such as adrenaline, which can aggravate tachycardia, should be avoided; phenylephrine, angiotensinamide, vasopressin, or dopamine may be given if there is evidence of inadequate perfusion of a vital organ.

Topical application of minoxidil may be associated with contact dermatitis, pruritus, local burning, and flushing; sufficient may be absorbed to produce systemic adverse effects. Changes in hair colour or texture may occur.

Effects on the eyes. Bilateral optic neuritis and retinitis occurred in a patient during treatment with minoxidil for hypertension after a renal transplant.[1] The patient was also taking prednisolone and azathioprine.

1. Gombos GM. Bilateral optic neuritis following minoxidil administration. *Ann Ophthalmol* 1983; **15:** 259–61.

Effects on the hair. The hypertrichosis frequently associated with oral minoxidil makes it generally unsuitable for women. There have also been reports of changes in hair colour.[1] In addition a case has been reported of increased hair loss, followed by subsequent regrowth of differently-coloured hair.[2] Substantial hair loss occurred in a woman after withdrawal of minoxidil and she had to wear a wig.[3]

Severe hypertrichosis has also been reported in 5 of 56 women applying minoxidil 5% solution topically for androgenetic alopecia.[4] Facial, arm, and leg hypertrichosis were reported 2 to 3 months after starting treatment. Hypertrichosis had disappeared 5 months after discontinuation of minoxidil.

1. Traub YM, *et al.* Treatment of severe hypertension with minoxidil. *Isr J Med Sci* 1975; **11:** 991–8.
2. Ingles RM, Kahn T. Unusual hair changes with minoxidil therapy. *Int J Dermatol* 1983; **22:** 120–2.
3. Kidwai BJ, George M. Hair loss with minoxidil withdrawal. *Lancet* 1992; **340:** 609–10.
4. Peluso AM, *et al.* Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; **136:** 118–20.

Effects on skeletal muscle. A polymyalgia syndrome, manifesting as fatigue, anorexia, weight loss, and severe pain in the shoulders and pelvic girdle, was seen in 4 men using topical minoxidil.[1] All symptoms improved within 2 to 4 weeks of stopping the drug. In 2 of the patients rechallenge produced a recurrence of symptoms.

1. Colamarino R, *et al.* Polymyalgia and minoxidil. *Ann Intern Med* 1990; **113:** 256–7.

Effects on the skin. Although skin reactions to systemic minoxidil do not appear to be common, cases of classic Stevens-Johnson syndrome have been reported.[1,2] The syndrome generally responds to withdrawal and corticosteroid therapy; in one case[1] subsequent rechallenge provoked a recurrence. In another patient an extensive erythematous weeping rash with lesions consistent with actinic keratosis also appeared to be due to minoxidil; bullous lesions recurred on re-exposure.[3] After topical application itching, scaling, flushing, and dermatitis have been the most common adverse effects; allergic contact dermatitis has been reported in rare instances.[4]

For other lesions associated with Kaposi's sarcoma and angioma, see Neoplasms, below, and for effects on the hair, see above.

1. DiSantis DJ, Flanagan J. Minoxidil-induced Stevens-Johnson syndrome. *Arch Intern Med* 1981; **141:** 1515.
2. Callen EC, *et al.* Stevens-Johnson syndrome associated with oral minoxidil: a case report. *J Nephrol* 2007; **20:** 91–3.
3. Ackerman BH, *et al.* Pruritic rash with actinic keratosis and impending exfoliation in a patient with hypertension managed with minoxidil. *Drug Intell Clin Pharm* 1988; **22:** 702–3.
4. Clissold SP, Heel RC. Topical minoxidil: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in alopecia areata and alopecia androgenetica. *Drugs* 1987; **33:** 107–22.

Neoplasms. Two haemorrhagic lesions with Kaposi's features appeared on the forehead, an unusual location for HIV-associated Kaposi's sarcoma, in an HIV-positive patient who had applied topical minoxidil there for 3 months.[1] In a healthy patient an angioma of the scalp developed after 2 months of topical minoxidil therapy. The patient had had a similar lesion as a baby. Minoxidil may induce angiogenesis or may stimulate endothelial cells, fibroblasts, and muscle cells to proliferate. Care should be taken when minoxidil is applied to the skin of people who are predisposed to neo-angiogenesis, or who are HIV-positive.

For other effects of minoxidil on the skin following topical application, see above.

1. Pavlovitch JH, *et al.* Angiogenesis and minoxidil. *Lancet* 1990; **336:** 889.

Precautions

Minoxidil is contra-indicated in phaeochromocytoma. It should be used with caution after a recent myocardial infarction, and in patients with pulmonary hypertension, angina pectoris, chronic heart failure, and significant renal impairment.

Topical application of minoxidil should be restricted to the scalp; it should not be applied to inflamed scalp skin or areas affected by psoriasis, severe sunburn, or severe excoriations, because of the risk of increased absorption. Patients being treated for hypertension should be monitored if topical minoxidil is used concurrently.

AIDS. For recommendations that topical minoxidil should be used with caution in HIV-positive patients, see Neoplasms under Adverse Effects, above.

Breast feeding. Study[1] of a breast-feeding mother showed that minoxidil was rapidly distributed into breast milk, achieving similar concentrations to those in the maternal plasma. No adverse effects were seen in the infant after 2 months and the American Academy of Pediatrics considers[2] that minoxidil is therefore usually compatible with breast feeding.

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.
2. 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 26/09/05)

Porphyria. Minoxidil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Pregnancy. A patient who took minoxidil, propranolol, and furosemide throughout pregnancy delivered a normal infant at 37 weeks. Pregnancy was uneventful.[1]

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.

Interactions

The antihypertensive effect of minoxidil may be enhanced by use of other hypotensive drugs. Severe orthostatic hypotension may occur if minoxidil and sympathetic blocking drugs such as guanethidine are given concurrently.

Topical minoxidil should not be used with other topical agents known to enhance absorption, such as corticosteroids, retinoids, or occlusive ointment bases.

Tretinoin. Percutaneous absorption of minoxidil is enhanced by tretinoin as a result of increased stratum corneum permeability.[1]

1. Ferry JJ, *et al.* Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther* 1990; **47:** 439–46.

Pharmacokinetics

About 90% of an oral dose of minoxidil is absorbed from the gastrointestinal tract. The plasma half-life is about 4.2 hours although the haemodynamic effect may persist for up to 75 hours, presumably due to accumulation at its site of action. Minoxidil is not bound to plasma proteins. It is distributed into breast milk. Minoxidil is extensively metabolised by the liver. It requires sulfation to become active, but the major metabolite is a glucuronide conjugate. Minoxidil is excreted predominantly in the urine mainly in the form of metabolites. Minoxidil and its metabolites are dialysable, although the pharmacological effect is not reversed.

About 0.3 to 4.5% of a topical dose of minoxidil is absorbed from intact scalp.

◊ References.

1. Pacifici GM, *et al.* Minoxidil sulphation in human liver and platelets: a study of interindividual variability. *Eur J Clin Pharmacol* 1993; **45:** 337–41.

Uses and Administration

Minoxidil is an antihypertensive that acts mainly by causing direct peripheral vasodilatation of the arterioles. It produces effects on the cardiovascular system similar to those of hydralazine (p.1307). Minoxidil is given orally for the treatment of severe hypertension unresponsive to standard therapy (p.1171). When applied topically to the scalp minoxidil may stimulate hair growth to a limited extent and is used in the treatment of alopecia.

In the treatment of **hypertension** minoxidil is given with a beta blocker, or with methyldopa, to diminish the cardiac-accelerating effects, and with a diuretic, usually a loop diuretic, to control oedema. After a single oral dose, the maximum hypotensive effect usually occurs after 2 to 3 hours, although the full effects may not occur until after 3 to 7 days of continuous treatment. An initial dose of 5 mg of minoxidil daily (or 2.5 mg daily in the elderly) is gradually increased at intervals of not less than 3 days to 40 or 50 mg daily according to response; in exceptional circumstances up to 100 mg daily has been given. If more rapid control of blood pressure is required, dosage changes may be made every 6 hours with careful monitoring. The daily dose may be given as a single dose or in 2 divided doses. For children, the initial dose is 200 micrograms/kg daily, increased in steps of 100 to 200 micrograms/kg at intervals of not less than 3 days, until control of blood pressure has been achieved or a maximum of 1 mg/kg or 50 mg daily has been reached.

Reduced doses may be required in patients with renal impairment (see below).

In the treatment of **alopecia androgenetica** (male-pattern baldness) 1 mL of a 2% or 5% solution of minoxidil is applied twice daily to the scalp. The 5% solution is not recommended for women.

Administration in renal impairment. A study of the pharmacokinetics of minoxidil in patients with varying degrees of renal impairment found that the non-renal clearance was also impaired as renal function worsened.[1] Substantial accumulation of