astatin is excreted in the faeces, as unabsorbed drug and via the bile, and about 20% is excreted in the urine.

◊ General reviews.

1. Quion JAV, Jones PH. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet* 1994; **27:** 94–103.
2. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet* 2000; **39:** 397–412.

Uses and Administration

Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394).

Pravastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), dysbetalipoproteinaemia (type III), and post-transplantation hyperlipidaemia. It is also used for cardiovascular risk reduction (p.1164), including primary prophylaxis in hypercholesterolaemic patients, and secondary prophylaxis, including prevention of stroke, in patients with clinically-evident ischaemic heart disease.

Pravastatin is given orally as the sodium salt; the usual dose is 10 to 40 mg of pravastatin sodium once daily at bedtime. The dose may be adjusted, according to response, at intervals of not less than 4 weeks. UK licensed product information states that the maximum dose is 40 mg once daily, but US licensed product information allows a maximum of 80 mg once daily in patients with hypercholesterolaemia. Low initial doses are recommended in patients with hepatic or renal impairment (see below).

In patients also taking *ciclosporin*, UK licensed product information recommends an initial dose of 20 mg once daily, but US licensed product information states an initial dose of 10 mg; dose increases should be made with caution.

For the use of pravastatin in children and adolescents, see below.

◊ General reviews.

1. McTavish D, Sorkin EM. Pravastatin: a review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1991; **42:** 65–89.
2. Haria M, McTavish D. Pravastatin: a reappraisal of its pharmacological properties and clinical effectiveness in the management of coronary heart disease. *Drugs* 1997; **53:** 299–336.

Administration in children. In children with heterozygous familial hypercholesterolaemia, pravastatin sodium is licensed in doses of 10 to 20 mg once daily in those aged 8 to 13 years and 10 to 40 mg once daily in those aged 14 to 18 years. Short-term studies have suggested that pravastatin effectively reduces cholesterol and is safe in children with familial hypercholesterolaemia[1] and in children taking immunosuppressants after heart transplant,[2] although plasma concentrations may be higher in the latter group. A randomised controlled study[3] and a prospective study[4] have also found that pravastatin is effective and well tolerated in familial hypercholesterolaemia, and there is some evidence[3] that carotid intima media thickness (a marker of atherosclerosis) may be reduced.

1. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther* 2003; **74:** 178–85.
2. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. *Clin Pharmacol Ther* 2004; **75:** 101–109.
3. Wiegman A, *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; **292:** 331–7.
4. Hedman M, *et al.* Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab* 2005; **90:** 1942–52.

Administration in hepatic or renal impairment. Patients with moderate or severe renal or significant hepatic impairment should be given pravastatin sodium in an initial dose of 10 mg daily, and the dose should be increased with caution.

Preparations

BP 2008: Pravastatin Tablets;
USP 31: Pravastatin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Pravacol; ***Austral.:*** Cholstat; Lipostat; Pravachol; ***Austria:*** Panchol; Pravachol; Sanaprav†; Selipran; ***Belg.:*** Merckprareduct; Prareduct†; Pravasine; ***Braz.:*** Mevalotin; Pravacol; ***Canad.:*** Pravachol; ***Chile:*** Pravacol; ***Cz.:*** Lipostat†; ***Denm.:*** Pravachol; ***Fin.:*** Pravachol; ***Fr.:*** Elisor; Vasten; ***Ger.:*** Mevalotin; Prava Basics; Pravabeta; Pravagamma; PravaLich; Pravalip; Pravasin; ***Gr.:*** Antisterin; Asto-Chol; Cholipravin; Cosivatin; Lipoprav; Maxudin; Ositron; Panlipol; Pravachol; Pravafact; Pravahelp; Pravalip; Pravalong; Pravanox; Pravedol; Pravin; Pravostin; Privast; Sosmin; Vastil; Zoter; Zyon; ***Hong Kong:*** Pravachol; ***Hung.:*** Nikron; Prastin; Pravastar; ***India:*** Pravator; ***Indon.:*** Cholespar; Koleskol; Mevachol; Novales; Pravachol; ***Irl.:*** ByStat; Cholstat; Lipostat; Pravamel; Pravat; Pravitin; ***Israel:*** Lipidal†; Pravalip; ***Ital.:*** Aplactin; Prasterol; Pravaselect; Sanaprav; Selectin; ***Jpn:*** Mevalotin; ***Malaysia:*** Pravachol; ***Mex.:*** Astin; Brakhor; Colpradin; Kenstatin; Kenvastin; Lexet; Loretsin; Mavitina; Novina; Paver; Prascolend; Prasiver; Pravacol; Striacol; Tissulest; Tratinal; Tridanil-H; Vaprasil; Varlex; Xipral; ***Neth.:*** Lipitifi; Lipratif; Pratiflip†; Pravandrea; Selektine; Statifil; Tifistat†; Vastatifix; ***Norw.:*** Pravachol; ***NZ:*** Lipostat; Pravachol; ***Philipp.:*** Lipostat; Stanidine; ***Pol.:*** Apo-Prava; ***Port.:*** Pravacol; Pritanol; Sanaprav; ***S.Afr.:*** Pranalip; Prava; ***Singapore:*** Pravachol; ***Spain:*** Bristacol; Lipemol; Liplat; Prareduct; Pravalipem†; Pritadol; ***Swed.:*** Pravachol; ***Switz.:*** Mevalotin; Pravalotin; Pravasta eco; Pravatine; Selipran; ***Thai.:*** Mevalotin; ***Turk.:*** Pravachol; ***UK:*** Lipostat; ***USA:*** Pravachol; ***Venez.:*** Mevalotin; Pravacol.

Multi-ingredient: ***Fr.:*** Pravadual; ***Neth.:*** Selektine Plus; ***USA:*** Pravigard PAC†.

Prazosin Hydrochloride

(BANM, USAN, rINNM)

CP-12299-1; Furazosin Hydrochloride; Hidrocloruro de prazosina; Pratsosiinihydrokloridi; Prazosin Hidroklorür; Prazosine, chlorhydrate de; Prazosin-hydrochlorid; Prazosinhydroklorid; Prazosini hydrochloridum; Prazozin-hidroklorid; Prazozino hidrochloridas. 2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine hydrochloride.

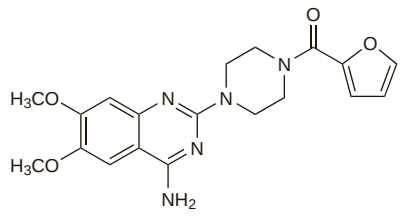
Празозина Гидрохлорид

$C_{19}H_{21}N_5O_4$,HCl = 419.9.

CAS — 19216-56-9 (prazosin); 19237-84-4 (prazosin hydrochloride).

ATC — C02CA01.

ATC Vet — QC02CA01.



(prazosin)

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

Ph. Eur. 6.2 (Prazosin Hydrochloride). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 31 (Prazosin Hydrochloride). A white to tan powder. Slightly soluble in water, in dimethylacetamide, in dimethylformamide, and in methyl alcohol; very slightly soluble in alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Adverse Effects

Prazosin hydrochloride can cause orthostatic hypotension which may be severe and produce syncope after the initial dose; it may be preceded by tachycardia. This reaction can be avoided by starting treatment with a low dose, preferably at night (see Uses and Administration, below). The hypotensive effects may be exaggerated by exercise, heat, or alcohol ingestion.

The more common adverse effects include dizziness, drowsiness, headache, lack of energy, nausea, and palpitations, and may diminish with continued prazosin therapy or with a reduction in dosage. Other adverse effects include oedema, chest pain, dyspnoea, constipation, diarrhoea, vomiting, depression and nervousness, sleep disturbances, vertigo, hallucinations, paraesthesia, nasal congestion, epistaxis, dry mouth, urinary frequency and incontinence, reddened sclera, blurred vision, tinnitus, abnormal liver enzyme values, pancreatitis, arthralgia, alopecia, lichen planus, skin rashes, pruritus, and diaphoresis. Impotence and priapism have also been reported.

◊ General reviews.

1. Carruthers SG. Adverse effects of α -adrenergic blocking drugs. *Drug Safety* 1994; **11:** 12–20.

Effects on the cardiovascular system. Orthostatic hypotension, preceded by tachycardia and sometimes producing syncope, is an established adverse effect of the initial dose of prazosin. Sinus bradycardia was associated with prazosin in a patient who had light headedness after each daily dose.[1]

1. Ball J. Symptomatic sinus bradycardia due to prazosin. *Lancet* 1994; **343:** 121.

Effects on the gastrointestinal tract. Faecal incontinence in a 52-year-old man receiving prazosin was exacerbated by haemorrhoidectomy and appeared to be due to diminished resting anal tone, presumably because of smooth muscle relaxation secondary to alpha-adrenoceptor blockade.[1] Symptoms ceased almost immediately on stopping the drug.

1. Holmes SAV, *et al.* Faecal incontinence resulting from α -adrenoceptor blockade. *Lancet* 1990; **336:** 685–6.

Effects on mental function. Psychiatric symptoms including confusion, paranoia, and hallucinations developed in 3 patients associated with prazosin treatment.[1] Two of the patients had chronic renal failure and the other had mild renal impairment. Acute psychosis has also been reported with doxazosin.[2]

1. Chin DKF, *et al.* Neuropsychiatric complications related to use of prazosin in patients with renal failure. *BMJ* 1986; **293:** 1347.
2. Evans M, *et al.* Drug induced psychosis with doxazosin. *BMJ* 1997; **314:** 1869.

Hypersensitivity. Urticaria and angioedema were attributed to prazosin in a 70-year-old woman.[1]

1. Ruzicka T, Ring J. Hypersensitivity to prazosin. *Lancet* 1983; **i:** 473–4.

Lupus erythematosus. One study has reported the formation of antinuclear antibodies in patients receiving prazosin,[1] but this is not in agreement with other reports,[2,3] and commentators consider the association unproven.[4] There is no evidence of the development of lupus erythematosus.[1]

1. Marshall AJ, *et al.* Positive antinuclear factor tests with prazosin. *BMJ* 1979; **1:** 165–6.
2. Wilson JD, *et al.* Antinuclear factor in patients on prazosin. *BMJ* 1979; **1:** 553–4.
3. Melkild A, Gaarder PI. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 620–1.
4. Kristensen BØ. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 621.

Urinary incontinence. There have been reports of urinary incontinence developing in patients receiving prazosin. Analysis[1] of 56 cases reported to the Australian Adverse Drug Reactions Advisory Committee indicated that typically symptoms appeared within 1 or 2 days of the start of therapy and persisted until the drug was withdrawn or the dose reduced. Both stress and urge incontinence occurred, sometimes in the same patient. Of the 56 patients, 51 were women and most were elderly. In a study[2] in women attending a hypertension clinic urinary incontinence was reported in 40.8% of 49 women receiving alpha blockers (prazosin, terazosin, or doxazosin) and in 16.3% of controls. Incontinence might be due to a reduction in urethral pressure induced by alpha-adrenoceptor blockade.

Interestingly, faecal incontinence has also been reported with prazosin—see Effects on the Gastrointestinal Tract, above.

1. Mathew TH, *et al.* Urinary incontinence secondary to prazosin. *Med J Aust* 1988; **148:** 305–6.
2. Marshall HJ, Beevers DG. α-Adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. *Br J Clin Pharmacol* 1996; **42:** 507–9.

Treatment of Adverse Effects

If overdosage with prazosin occurs activated charcoal should be given if the patient presents within 1 hour of ingestion. Severe hypotension may occur and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement, and if necessary cautious intravenous infusion of a vasopressor. Prazosin is not removed by dialysis.

Precautions

Treatment with prazosin should be introduced cautiously because of the risk of sudden collapse following the initial dose. Extra caution is necessary in patients with hepatic or renal impairment and in the elderly.

Prazosin is not recommended for the treatment of heart failure caused by mechanical obstruction, for example aortic or mitral valve stenosis, pulmonary embolism, and restrictive pericardial disease. It should be used with caution in patients with angina pectoris. Prazosin may cause drowsiness or dizziness; patients so affected should not drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Surgical Procedures under Precautions for Tamsulosin Hydrochloride, p.2197.

Cerebral haemorrhage. Hypotension with disturbance of consciousness[1] occurred in 3 patients with recent cerebral haemorrhage after an initial dose of prazosin 500 micrograms.

1. Lin M-S, Hsieh W-J. Prazosin-induced first-dose phenomenon possibly associated with hemorrhagic stroke: a report of three cases. *Drug Intell Clin Pharm* 1987; **21:** 723–6.

Tolerance. Although prazosin may be of initial benefit in patients with chronic heart failure, some studies[1,2] have reported the development of tolerance to its haemodynamic effects on prolonged therapy. This may be partly due to upregulation of alpha$_1$ adrenoceptors.[3]

1. Packer M, *et al*. Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. *J Am Coll Cardiol* 1986; **7:** 671–80.
2. Bayliss J, *et al.* Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. *BMJ* 1985; **290:** 1861–5.
3. Kersting F, *et al.* Preliminary evidence for the mechanism underlying the development of tolerance to prazosin in congestive heart failure: the α-agonistic properties of dobutamine unmasked by prazosin treatment. *J Cardiovasc Pharmacol* 1993; **21:** 537–43.

Interactions

The hypotensive effects of prazosin may be enhanced by use with diuretics and other antihypertensives, and by alcohol and other drugs that cause hypotension. The risk of first-dose hypotension may be particularly increased in patients receiving beta blockers or calcium-channel blockers.

Analgesics. *Indometacin* reduced prazosin-induced hypotension in 4 of 9 subjects.[1]

1. Rubin P, *et al*. Studies on the clinical pharmacology of prazosin II: the influence of indomethacin and of propranolol on the action and disposition of prazosin. *Br J Clin Pharmacol* 1980; **10:** 33–9.

Antidepressants and antipsychotics. A patient who was taking *amitriptyline* and *chlorpromazine* developed acute agitation on receiving prazosin.[1] The symptoms settled rapidly when prazosin was discontinued. Antidepressants and antipsychotics may enhance the hypotensive effect of prazosin and other alpha blockers.

1. Bolli P, Simpson FO. New vasodilator drugs for hypertension. *BMJ* 1974; **1:** 637.

Calcium-channel blockers. An enhanced hypotensive effect has been reported in normotensive subjects given prazosin and *verapamil* concurrently; the effect may be due in part to enhanced bioavailability of prazosin.[1] Markedly increased hypotensive responses have also been reported with combined use of prazosin and *nifedipine*,[2,3] although the validity of such reports has been questioned.[4]

1. Pasanisi F, *et al*. Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. *Clin Pharmacol Ther* 1984; **36:** 716–23.
2. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. *BMJ* 1983; **287:** 1514.
3. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238–9.
4. Elliott HL, *et al*. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238.

Digoxin. For reference to the effect of prazosin on serum-digoxin concentrations, see under Digoxin, p.1261.

Pharmacokinetics

Prazosin is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 to 3 hours after an oral dose. The bioavailability is variable and a range of 43 to 85% has been reported. Prazosin is highly bound to plasma proteins. It is extensively metabolised in the liver and some of the metabolites are reported to have hypotensive activity. It is excreted as the metabolites and 5 to 11% as unchanged prazosin mainly in the faeces via the bile. Less than 10% is excreted in the urine. Small amounts are distributed into breast milk. Its duration of action is longer than would be predicted from its relatively short plasma half-life of about 2 to 4 hours. Half-life is reported to be increased to about 7 hours in patients with heart failure.

The elderly. The bioavailability of prazosin was significantly reduced in the elderly, about 40% less unchanged drug reaching the systemic circulation compared with the young.[1] This was attributed to a reduction in the absorption from the gastrointestinal tract. The half-life was also prolonged in the elderly and this was associated with an increase in the volume of distribution at steady state. However, it was considered unlikely that these effects would have major clinical significance.

1. Rubin PC, *et al*. Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol* 1981; **12:** 401–4.

Protein binding. Although a study[1] found that prazosin was about 80 to 85% bound to serum albumin and only about 10 to 30% bound to α_1-acid glycoprotein *in vitro*, potential interactions between the binding proteins *in vivo* were not taken into account; binding to α_1-acid glycoprotein might be more significant in clinical practice. A subsequent study[2] indicated that variations in prazosin protein binding pre- and post-operatively were related to variations in concentration of the glycoprotein.

1. Brunner F, Müller WE. Prazosin binding to human α -acid glycoprotein (orosomucoid), human serum albumin, and human serum: further characterisation of the 'single drug binding site' of orosomucoid. *J Pharm Pharmacol* 1985; **37:** 305–9.
2. Sager G, *et al.* Binding of prazosin and propranolol at variable α -acid glycoprotein and albumin concentrations. *Br J Clin Pharmacol* 1989; **27:** 229–34.

Uses and Administration

Prazosin is an alpha blocker (p.1153) that acts by selective blockade of alpha$_1$-adrenoceptors. It is used in the management of hypertension (p.1171), in Raynaud's syndrome (see Peripheral Vascular Disease, below), and to relieve symptoms of urinary obstruction in benign prostatic hyperplasia (p.2178). It has also been used in heart failure (p.1165).

Prazosin produces peripheral dilatation of both arterioles and veins and reduction of peripheral resistance, usually without reflex tachycardia. It reduces both standing and supine blood pressure with a greater effect on the diastolic pressure. It is reported to have no effect on renal blood flow or glomerular filtration rate, and has little effect on cardiac output in hypertensive patients. In patients with heart failure, prazosin reduces both preload and afterload and produces an improvement in cardiac output, although tolerance may develop. In benign prostatic hyperplasia, prazosin may relieve the symptoms of urinary obstruction by reducing smooth muscle tone in the prostate and bladder neck.

Prazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Prazosin hydrochloride 1.1 mg is equivalent to about 1 mg of prazosin. After oral dosage the hypotensive effect is seen within 2 to 4 hours and persists for several hours. Full effects are seen after 4 to 6 weeks.

A low starting dose is given in the evening to lessen the risk of collapse which may occur in some patients after the first dose (see Adverse Effects, above). Doses may need to be reduced in the elderly and in patients with hepatic or renal impairment.

In **hypertension**, the usual initial dose in the UK is 500 micrograms two or three times daily for 3 to 7 days; if tolerated the dose may then be increased to 1 mg two or three times daily for a further 3 to 7 days, and thereafter gradually increased, according to the patient's response, to a usual maximum of 20 mg daily in divided doses. In the US the recommended starting dose is 1 mg two or three times daily and up to 40 mg daily in divided doses has been given; however, the usual maintenance dose is between 6 and 15 mg daily. Smaller doses may be required in patients also taking other antihypertensives. Modified-release preparations may allow once daily dosing.

In **Raynaud's syndrome** and in **benign prostatic hyperplasia** an initial dose of 500 micrograms twice daily may be given, increasing to a maintenance dose not exceeding 2 mg twice daily.

In **heart failure**, treatment has been started with 500 micrograms two to four times daily and increased gradually according to response; the usual maintenance dose has been 4 to 20 mg daily.

Erectile dysfunction. Prazosin has been given transurethrally with alprostadil[1] in the management of erectile dysfunction (p.2179).

1. Peterson CA, *et al.* Erectile response to transurethral alprostadil, prazosin and alprostadil-prazosin combinations. *J Urol (Baltimore)* 1998; **159:** 1523–8.

Familial Mediterranean fever. Familial Mediterranean fever (p.557) is usually treated with prophylactic colchicine, but its use may be limited by adverse effects. A Japanese man who had suffered from attacks for 16 years was treated[1] with prazosin 3 mg daily. There were no further attacks for more than a year after starting treatment, but stopping prazosin resulted in a recurrence.

1. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.

Muscle cramp. Skeletal muscle cramp may occur during haemodialysis, possibly due to activation of the sympathetic nervous system. Prazosin was reported[1] to reduce the incidence of cramp in 4 of 5 patients with frequent haemodialysis-associated muscle cramp. However, the increased incidence of hypotension reported might limit its use for this indication.

1. Sidhom OA, *et al.* Low-dose prazosin in patients with muscle cramps during hemodialysis. *Clin Pharmacol Ther* 1994; **56:** 445–51.

Peripheral vascular disease. Alpha blockers, including prazosin, may be used in the management of Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188). Studies of the benefits of prazosin have produced varying results. A short-term reduction in number and duration of attacks was reported in 5 of 7 patients given prazosin 2 mg daily but only 1 patient had complete relief from attacks and few could tolerate doses higher than 6 mg daily.[1] Improvements were not maintained during continued treatment for 2 months. Others[2,3] have reported benefit from prazosin 1 mg two or three times daily in the majority of patients, with one study suggesting greater benefit in Raynaud's disease (the primary, idiopathic form) than in secondary Raynaud's syndrome.[2] In a subsequent study, higher doses of prazosin (2 or 4 mg three times daily) were no more effective than 1 mg three times daily, and were associated with a significantly greater incidence of adverse effects.[4] A systematic review[5] concluded that prazosin was modestly effective in the treatment of Raynaud's syndrome secondary to scleroderma.

1. Nielsen SL, *et al.* Prazosin treatment of primary Raynaud's phenomenon. *Eur J Clin Pharmacol* 1983; **24:** 421–3.
2. Allegra C, *et al.* Pharmacological treatment of Raynaud's phenomenon: a new therapeutic approach. *Curr Ther Res* 1986; **40:** 303–11.
3. Wollersheim H, *et al.* Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986, **40:** 219–25.
4. Wollersheim H, Thien T. Dose-response study of prazosin in Raynaud's phenomenon: clinical effectiveness versus side effects. *J Clin Pharmacol* 1988; **28:** 1089–93.
5. Pope J, *et al.* Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 24/06/05).

Post-traumatic stress disorder. Post-traumatic stress disorder (p.953) is usually treated with psychotherapy or drugs such as SSRIs. Increased alpha$_1$-adrenergic receptor activity may be a contributory factor, and several small studies have reported that treatment with prazosin improves nightmares and sleep disturbances in patients with this condition.[1,2] A reduction in nightmares occurred in 5 patients taking part in a small 6-week open-label study;[3] doses ranged from 1 mg at night to 2 mg night and morning. A similar improvement was found in a retrospective study[4] of combat veterans with chronic treatment-resistant symptoms, where doses of prazosin were increased gradually from 1 mg at night up to a maximum daily dose of 20 mg if required, and in a placebo-controlled study[5] in similar patients given doses of up to 15 mg at night. Another small study[6] and a case report[7] have also reported benefit; doses varied from 1 mg at night to 10 mg daily in 2 divided doses.

1. Dierks MR, *et al.* Prazosin treatment of nightmares related to posttraumatic stress disorder. *Ann Pharmacother* 2007; **41:** 1013–17.
2. Taylor HR, *et al.* Prazosin for treatment of nightmares related to posttraumatic stress disorder. *Am J Health-Syst Pharm* 2008; **65:** 716–22.
3. Taylor F, Raskind MA. The α -adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 82–5.
4. Raskind MA, *et al.* Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2002; **63:** 565–8.
5. Raskind MA, *et al.* A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 2007; **61:** 928–34.
6. Raskind MA, *et al.* Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003; **160:** 371–3.
7. Griffith LJ. Case report: use of prazosin for treatment of post-traumatic stress disorder. *Am Fam Physician* 2005; **72:** 758, 761.

Renal calculi. For the potential use of alpha blockers to aid the passage of renal calculi, see under Uses of Tamsulosin Hydrochloride, p.2197.

Scorpion stings. Stings from the Indian red scorpion (*Mesobuthus tamulus*) are potentially fatal. The scorpion venom is a potent sympathetic stimulator resulting in high circulating catecholamines, hypertension, arrhythmias, pulmonary oedema, and circulatory failure. The efficacy of antivenom is questionable and treatment for cardiotoxicity is supportive (see p.2237). Prazosin, given orally, appears to be beneficial and has been suggested[1,2] as first-line treatment, except in cases of severe pulmonary oedema. Prazosin has also been used in other countries to treat stings by dangerous scorpion species.[3,4]

1. Bawaskar HS, Bawaskar PH. Scorpion envenoming and the cardiovascular system. *Trop Doct* 1997; **27:** 6–9.
2. Bawaskar HS, Bawaskar PH. Utility of scorpion antivenin vs prazosin in the management of severe Mesobuthus tamulus (Indian red scorpion) envenoming at rural setting. *J Assoc Physicians India* 2007; **55:** 14–21.
3. Koseoglu Z, Koseoglu A. Use of prazosin in the treatment of scorpion envenomation. *Am J Ther* 2006; **13:** 285–7.
4. Al-Asmari AK, *et al.* Role of prazosin on cardiovascular manifestations and pulmonary edema following severe scorpion stings in Saudi Arabia. *Saudi Med J* 2008; **29:** 299–302.

Preparations

BP 2008: Prazosin Tablets;
USP 31: Prazosin Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Decliten; Minipres†; ***Austral.:*** Minipress; Prasig†; Pratsiol; Prazohexal†; Pressin; ***Austria:*** Minipress; ***Belg.:*** Minipress; ***Braz.:*** Minipress; ***Canad.:*** Apo-Prazo; Minipress; Novo-Prazin; Nu-Prazo; ***Cz.:*** Deprazolin; ***Denm.:*** Hexapress; Peripress†; Prazac; ***Fin.:*** Peripress†; Pratsiol; ***Fr.:*** Alpress; Minipress; ***Ger.:*** Adversuten†; duramipress†; Minipress; ***Hong Kong:*** Apo-Prazo; CP-Prazo; Minipress; Mizosin; ***Hung.:*** Huma-Prazin†; Minipress; ***India:*** Minipress; Prazocip; ***Irl.:*** Hypovase; ***Israel:*** Hypotens; ***Jpn:*** Minipress†; ***Malaysia:*** Atodel; Minipress; Minison; ***Mex.:*** Anapres; Ensibest; Minipres; Sinozzard; ***NZ:*** Apo-Prazo; Hyprosin; Pratsiol; ***Pol.:*** Polpressin†; ***S.Afr.:*** Minipress†; Pratsiol; ***Singapore:*** Apo-Prazo; Minipress; ***Spain:*** Minipres; ***Switz.:*** Minipress†; ***Thai.:*** Atodel; Lopress; Minipress; Parabowl†; Polypress; Pratsiol†; Pressin; ***Turk.:*** Minipress; ***UK:*** Hypovase; Kentovase†; ***USA:*** Minipress; ***Venez.:*** Minpres.

Multi-ingredient: ***Ger.:*** Polypress†; ***USA:*** Minizide†.

Prenalterol Hydrochloride *(BANM, USAN, rINNM)*

C-50005/A-Ba (racemate); CGP-7760B; H133/22; H-80/62 (racemate); Hidrocloruro de prenalterol; Prénaltérol, Chlorhydrate de; Prenalteroli Hydrochloridum. (*S*)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

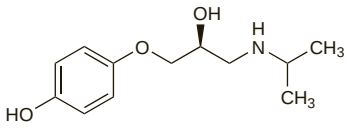
Пренальтерола Гидрохлорид

$C_{12}H_{19}NO_3$,HCl = 261.7.

CAS — 57526-81-5 (prenalterol); 61260-05-7 (prenalterol hydrochloride).

ATC — C01CA13.

ATC Vet — QC01CA13.



(prenalterol)

Profile

Prenalterol is a sympathomimetic (p.1407) with stimulant effects on beta$_1$ adrenoceptors. It has an inotropic action on the heart with relatively little chronotropic effect. Prenalterol hydrochloride has been given parenterally in the treatment of heart failure and shock. It has also been promoted for the reversal of beta blockade.

Probucol *(BAN, USAN, rINN)*

DH-581; Probucolum. 4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol).

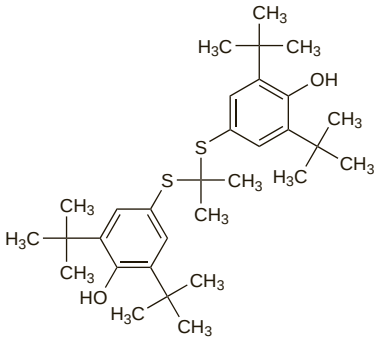
Пробукол

$C_{31}H_{48}O_2S_2$ = 516.8.

CAS — 23288-49-5.

ATC — C10AX02.

ATC Vet — QC10AX02.



Pharmacopoeias. In *Chin.* and *US*.

USP 31 (Probucol). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in petroleum spirit; freely soluble in chloroform and in propyl alcohol. Protect from light.

Profile

Probucol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p.1169). It lowers total plasma-cholesterol concentrations, mainly by reducing low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol concentrations but has little effect on triglyceride or very-low-density lipoprotein (VLDL)-cholesterol concentrations. It has also been used to prevent restenosis after reperfusion and revascularisation procedures (below), and in scleroderma.

Probucol prolongs the QT interval and has been associated with cardiac arrhythmias.

Reperfusion and revascularisation procedures. Restenosis is common after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Probucol, started a few weeks before the procedure, has been reported to reduce the rate of restenosis after coronary angioplasty,[1] and to reduce the need for repeat interventions,[1,2] although another study[3] found no effect.

1. Tardif J-C, *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997; **337:** 365–72.
2. Daida H, *et al.* Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). *Am J Cardiol* 2000; **86:** 550–2.
3. Nunes GL, *et al.* Role of probucol in inhibiting intimal hyperplasia after coronary stent implantation: a randomized study. Abstract: *Am Heart J* 2006; **152:** 914. Full version: http://www.ahjonline.com/article/S0002-8703(06)00463-7/pdf (accessed 07/08/07)

Preparations

USP 31: Probucol Tablets.

Proprietary Preparations (details are given in Part 3)
Mex.: Serterol†; ***Port.:*** Lisosterol; ***S.Afr.:*** Lurselle†; ***Spain:*** Superlipid†; ***Thai.:*** Lurselle†.

Procainamide Hydrochloride

(BANM, rINNM)

Hidrocloruro de procainimida; Novocainamidum; Procaïnamide, chlorhydrate de; Procainamidi Chloridum; Procainamidi hydrochloridum; Prokaiinamidihydrokloridi; Prokainamid-hidroklorid; Prokainamid-hydrochlorid; Prokainamidhydroklorid; Prokainamido hidrochloridas; Prokainamidu chlorowodorek. 4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride.

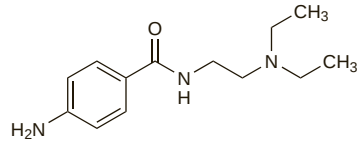
Прокаинамида Гидрохлорид

$C_{13}H_{21}N_3O$,HCl = 271.8.

CAS — 51-06-9 (procainamide); 614-39-1 (procainamide hydrochloride).

ATC — C01BA02.

ATC Vet — QC01BA02.



(procainamide)

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

Ph. Eur. 6.2 (Procainamide Hydrochloride). A white or very slightly yellow, hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 5.6 to 6.3. Store in airtight containers. Protect from light.

USP 31 (Procainamide Hydrochloride). A white to tan, odourless, crystalline powder. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether and in benzene. A 10% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Procainamide is more stable in neutral solutions such as sodium chloride, than in acidic solutions such as glucose, but patients requiring intravenous procainamide often have heart failure and cannot tolerate the sodium load associated with sodium chloride injections. The stability of procainamide in glucose 5% is improved by neutralising the glucose using sodium bicarbonate, or storing the admixture at 5°. The concentration of procainamide remained above 90% of the initial concentration for 24 hours if the glucose was first neutralised and this was considered more practical than refrigeration if extended stability was required.[1]

The compound formed by mixing procainamide hydrochloride with glucose 5% was shown to be a mixture of α- and β-glucosylamines[2] and about 10 to 15% of the procainamide was lost in this way after 10 hours at room temperature.

An oral liquid,[3] prepared from procainamide capsules, containing 5, 50, or 100 mg/mL of the hydrochloride was stable for at least 6 months when stored at 4° to 6°.

1. Raymond GG, *et al.* Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988; **45:** 2513–17.
2. Sianipar A, *et al.* Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994; **46:** 951–5.
3. Metras JI, *et al.* Stability of procainamide hydrochloride in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1992; **49:** 1720–4.

Adverse Effects

Cardiac effects occur particularly during intravenous use of procainamide and in overdose. Rapid intravenous dosage may result in severe hypotension, ventricular fibrillation, and asystole. High plasma concentrations are also associated with impaired cardiac conduction.

Hypersensitivity reactions to procainamide are common. Procainamide is a frequent cause of drug-induced SLE and the incidence has been reported to be as high as 30% during long-term use. Antinuclear antibodies may be detected in a high proportion of patients, but they do not necessarily develop the symptoms of SLE, which include arthralgia, arthritis, myalgia, pleural effusion, pericarditis, and fever. Agranulocytosis, eosinophilia, neutropenia, thrombocytopenia, and haemolytic anaemia have been reported. Other symptoms of hypersensitivity not necessarily related to SLE may also occur including hepatomegaly, angioedema, skin rashes, pruritus, urticaria, flushing, and hypergammaglobulinaemia.

Anorexia, nausea, vomiting, a bitter taste, and diarrhoea are more common with higher oral doses. Effects on the CNS such as mental depression, dizziness, and psychosis with hallucinations, have been reported.

Incidence of adverse effects. Out of 488 hospitalised patients in the Boston Collaborative Drug Surveillance Program who had received procainamide, 45 had acute adverse effects attributed to the drug.[1] Life-threatening reactions included heart block (3), tachyarrhythmias (2), and bradycardia and/or hypotension (2). Other reactions included gastrointestinal upsets (19), pyrexia (8), bradycardia and hypotension (5), tachyarrhythmias (3), heart block (1), eosinophilia (1), and urticaria (1).

1. Lawson DH, Jick H. Adverse reactions to procainamide. *Br J Clin Pharmacol* 1977; **4:** 507–11.

Effects on the blood. Adverse haematological effects reported during procainamide therapy include neutropenia,[1-3] agranulocytosis,[2-6] thrombocytopenia,[5] haemolytic anaemia,[7] and pancytopenia.[8] These disorders are usually reversible on withdrawing procainamide although some fatalities have been reported.[3,4] It has been suggested[2,6] that agranulocytosis or severe neutropenia is more likely in patients taking modified-release preparations, but others have found no difference in the incidence between modified-release and conventional-release preparations.[3] An increased risk of agranulocytosis with procainamide has been documented in one large study.[9] Although the precise estimate of excess risk could not be calculated, the order of magnitude was about 3 per million exposed for up to one week. This excess risk was low and of little relevance in the initial choice of therapy.

1. Riker J, *et al.* Bone marrow granulomas and neutropenia associated with procainamide. *Arch Intern Med* 1978; **138:** 1731–2.
2. Ellrodt AG, *et al.* Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 1984; **100:** 197–201.
3. Meyers DG, *et al.* Severe neutropenia associated with procainamide: comparison of sustained release and conventional preparations. *Am Heart J* 1985; **109:** 1393–5.
4. Fleet S. Agranulocytosis, procainamide, and phenytoin. *Ann Intern Med* 1984; **100:** 616–17.
5. Christensen DJ, *et al.* Agranulocytosis, thrombocytopenia, and procainamide. *Ann Intern Med* 1984; **100:** 918.
6. Thompson JF, *et al.* Procainamide agranulocytosis: a case report and review of the literature. *Curr Ther Res* 1988; **44:** 872–81.
7. Kleinman S, *et al.* Positive direct antiglobulin tests and immune hemolytic anemia in patients receiving procainamide. *N Engl J Med* 1984; **311:** 809–12.
8. Bluming AZ, *et al.* Severe transient pancytopenia associated with procainamide ingestion. *JAMA* 1976; **236:** 2520–1.
9. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects on the gastrointestinal tract. Pseudo-obstruction of the bowel occurred in a diabetic patient when given procainamide both orally and intravenously. It was believed that the anticholinergic properties of procainamide, together with the diabetic state, contributed to the severe hypomotility of the gastrointestinal tract.[1]

1. Peterson AM, *et al.* Procainamide-induced pseudo-obstruction in a diabetic patient. *DICP Ann Pharmacother* 1991; **25:** 1334–5.

Effects on the heart. Procainamide prolongs the QT interval and has been associated with the development of torsade de pointes,[1,2] and fatal cardiovascular toxicity has been reported[3] in patients with renal impairment. Toxicity appears to be related to accumulation of the major metabolite, *N*-acetylprocainamide, and haemodialysis has been used to reduce plasma concentrations and control symptoms,[1,4] although its benefits have been disputed (see Dialysis, under Treatment of Adverse Effects,