## 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†.

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## 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.

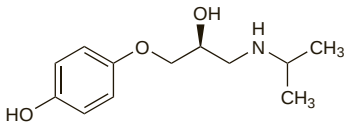
Пренальтерола Гидрохлорид

$C_{12}H_{19}NO_3$,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.

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

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

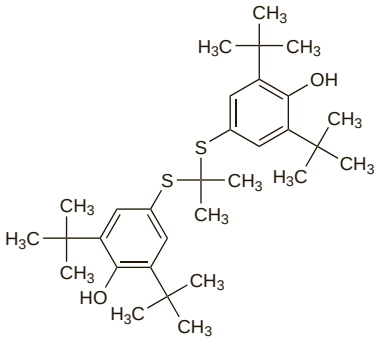
Пробукол

$C_{31}H_{48}O_2S_2$ = 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†.

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# 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.

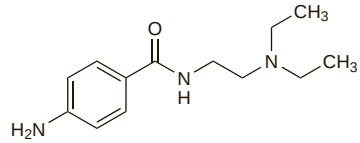
Прокаинамида Гидрохлорид

$C_{13}H_{21}N_3O$,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,