Bioavailability. Modified-release procainamide preparations have been shown[1] to produce similar steady-state serum concentrations of procainamide and *N*-acetylprocainamide when compared with equivalent total doses of immediate-release capsules. However, tablet matrices of a modified-release preparation have been recovered from the stools of a patient with diarrhoea[2] and 3.5 g of procainamide was recovered in these matrices over an 18-hour collection period; the patient had correspondingly low plasma-procainamide concentrations.

1. Vlasses PH, *et al.* Immediate-release and sustained-release procainamide: bioavailability at steady state in cardiac patients. *Ann Intern Med* 1983; **98:** 613–14.
2. Woosley RL, *et al.* Antiarrhythmic therapy: clinical pharmacology update. *J Clin Pharmacol* 1984; **24:** 295–305.

The elderly. Reduced renal clearance of procainamide has been reported in the elderly.[1,2]

1. Reidenberg MM, *et al.* Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharmacol Ther* 1980; **28:** 732–5.
2. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.

Hepatic impairment. In 20 healthy subjects and 20 patients with chronic liver disease given a single 500-mg oral dose of procainamide hydrochloride about 64 and 33% respectively of the dose was excreted in the urine within 6 hours.[1] Decreased procainamide acetylation in the patients compared with the control group was not correlated with the severity of liver disease, whereas decreased procainamide hydrolysis and increased procainamide-derived aminobenzoic acid acetylation appeared to be related to the degree of hepatic impairment. It was suggested that the decrease in excretion of procainamide and its metabolites in the urine of the patients with liver disease could be due to an impairment in oral absorption since renal function was within the normal range but the variations in acetylation and hydrolysis were related to hepatic function.

1. du Souich P, Erill S. Metabolism of procainamide and p-aminobenzoic acid in patients with chronic liver disease. *Clin Pharmacol Ther* 1977; **22:** 588–95.

Renal impairment. Procainamide and its active *N*-acetyl metabolite are mainly excreted in the urine and accumulation, particularly of the metabolite, may occur in renal impairment. A study[1] in 20 patients found that procainamide clearance correlated with renal function, and that the ratio of *N*-acetylprocainamide to procainamide in the serum increased as renal function declined. Fatal toxicity in patients with renal impairment and plasma-procainamide concentrations within the therapeutic range has been attributed[2] to accumulation of *N*-acetylprocainamide. Both procainamide and *N*-acetylprocainamide are removed by dialysis, although the benefit of these procedures has been disputed (see Dialysis under Treatment of Adverse Effects, above).

1. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.
2. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.

Uses and Administration

Procainamide is a class Ia antiarrhythmic (p.1153); it has properties similar to those of quinidine (p.1385).

Procainamide is usually reserved for the short-term management of severe or symptomatic ventricular arrhythmias (p.1160) such as those following myocardial infarction. It may also be used for cardioversion and management of atrial fibrillation.

Therapeutic effect is generally associated with plasma concentrations of 3 to 10 micrograms/mL. The dose of procainamide hydrochloride required will depend on the age, renal and hepatic function, and underlying cardiac condition of the patient: an adult with normal renal function generally requires up to 50 mg/kg daily in divided oral doses every 3 to 6 hours. Higher doses may be necessary for atrial arrhythmias. Modified-release preparations are available.

In an emergency and under continuous ECG and blood pressure monitoring, procainamide hydrochloride may be given intravenously. The injection should be diluted in glucose 5% to permit better control of the speed of injection, and should be given in doses of 100 mg every 5 minutes at a rate not exceeding 50 mg/minute until the arrhythmia has been suppressed or a maximum dose of 1 g has been reached. A response may be obtained after 100 to 200 mg has been given and more than 500 or 600 mg is not generally required. Alternatively, procainamide hydrochloride may be given by continuous infusion of 500 to 600 mg over 25 to 30 minutes. Therapeutic plasma concentrations may then be maintained by infusion at a rate of 2 to 6 mg/minute. When transferring to oral therapy, a period of about 3 to 4 hours should elapse between the last intravenous dose and the first oral dose.

Procainamide hydrochloride has also been given intramuscularly.

Procainamide hydrochloride may need to be given in reduced doses or at longer dosing intervals in the elderly and in patients with hepatic or renal impairment. For use in children, see below.

Acecainide (*N*-acetylprocainamide), the active metabolite of procainamide, has class III antiarrhythmic activity and has been used in ventricular arrhythmias.

Administration in children. In a study in 5 children treated with procainamide for various cardiac arrhythmias the mean elimination half-life was found to be 1.7 hours, and the plasma clearance was higher than that reported in adults.[1] In contrast the total serum clearance of procainamide in 3 neonates with supraventricular tachycardia was found to be similar to that in adults and the mean elimination half-life was 5.3 hours.[2] A loading dose of 10 to 12 mg/kg intravenously was given followed by a continuous infusion of 20 to 75 micrograms/kg per minute.

An oral dose of 15 to 50 mg/kg daily in 4 divided doses has been used in children.

1. Singh S, *et al.* Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 1982; **32:** 607–11.
2. Bryson SM, *et al.* Therapeutic monitoring and pharmacokinetic evaluation of procainamide in neonates. *DICP Ann Pharmacother* 1991; **25:** 68–71.

Preparations

BP 2008: Procainamide Injection; Procainamide Tablets;
USP 31: Procainamide Hydrochloride Capsules; Procainamide Hydrochloride Extended-release Tablets; Procainamide Hydrochloride Injection; Procainamide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pronestyl; ***Braz.:*** Procamide; ***Canad.:*** Procan; Pronestyl†; ***Gr.:*** Pronestyl; ***Hong Kong:*** Pronestyl†; ***India:*** Pronestyl; ***Irl.:*** Pronestyl; ***Israel:*** Pronestyl†; ***Neth.:*** Pronestyl; ***NZ:*** Pronestyl; ***S.Afr.:*** Pronestyl; ***Spain:*** Biocoryl; ***UK:*** Pronestyl†; ***USA:*** Procanbid.

Propafenone Hydrochloride

(BANM, USAN, rINNM)

Fenopraine Hydrochloride; Hidrocloruro de propafenona; Propafenon Hidroklorür; Propafénone, chlorhydrate de; Propafenon-hydrochlorid; Propafenonhydroklorid; Propafenoni hydrochloridum; Propafenonihydrokloridi; Propafenono hidrochloridas; SA-79; WZ-884642; WZ-884643. 2′-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride.

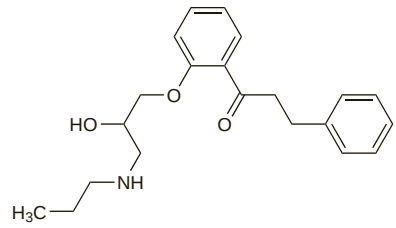
Пропафенона Гидрохлорид

$C_{21}H_{27}NO_3$,HCl = 377.9.

CAS — 54063-53-5 (propafenone); 34183-22-7 (propafenone hydrochloride).

ATC — C01BC03.

ATC Vet — QC01BC03.



(propafenone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Propafenone Hydrochloride). Colourless crystals or a white or almost white powder. Slightly soluble in cold water; soluble in hot water and in methyl alcohol; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.0 to 6.2.
USP 31 (Propafenone Hydrochloride). A white powder. Soluble in hot water and in methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in ether and in toluene. A 0.5% solution in water has a pH of 5.0 to 6.2. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Adverse Effects

Propafenone can cause disturbances in cardiac conduction which can result in bradycardia, heart block, and sinus arrest. It may aggravate heart failure and may cause hypotension. In common with other antiarrhythmics, propafenone may induce or worsen arrhythmias in some patients.

Among the most common adverse effects are gastrointestinal intolerance, dry mouth, a bitter or metallic taste, dizziness, blurred vision, headache, and fatigue. Convulsions, blood dyscrasias, liver disorders, lupus erythematosus, skin rashes, impotence, and increased breathlessness and worsening of asthma have also been reported.

Effects on the heart. Propafenone may worsen ventricular arrhythmias and there have been reports[1,2] of fatal exacerbations occurring hours to days after starting treatment. Cardiovascular toxicity may also occur in overdosage.[3] Torsade de pointes has been reported[2,4,5] but appears to be less frequent than with class Ia antiarrhythmics.

1. Nathan AW, *et al.* Fatal ventricular tachycardia in association with propafenone, a new class IC antiarrhythmic agent. *Postgrad Med J* 1984; **60:** 155–6.
2. Buss J, *et al.* Malignant ventricular tachyarrhythmias in association with propafenone treatment. *Eur Heart J* 1985; **6:** 424–8.
3. Clarot F, *et al.* Fatal propafenone overdoses: case reports and a review of the literature. *J Anal Toxicol* 2003; **27:** 595–9.
4. Rosengarten M, Brooks R. Torsade de pointes ventricular tachycardia in a hypothyroid patient treated with propafenone. *Can J Cardiol* 1987; **3:** 234–9.
5. Hii JT, *et al.* Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol* 1991; **14:** 1568–70.

Effects on the liver. A review of liver injury secondary to propafenone therapy concluded that it is a rare occurrence and appears to be due to hepatocellular injury, cholestasis, or a combination.[1]

1. Spinler SA, *et al.* Propafenone-induced liver injury. *Ann Pharmacother* 1992; **26:** 926–8.

Effects on mental function. Delusions, hallucinations, and paranoia have been reported in an elderly patient after 2 doses of propafenone. The manufacturer had received reports of mania and psychosis.[1] Amnesia developed in a 61-year-old man 6 days after starting treatment with propafenone.[2] Symptoms resolved 6 to 7 hours after stopping the drug.

1. Robinson AJ. Paranoia after propafenone. *Pharm J* 1991; **247:** 556.
2. Jones RJ, *et al.* Probable propafenone-induced transient global amnesia. *Ann Pharmacother* 1995; **29:** 586–90.

Effects on the nervous system. Myoclonus has been reported in a patient receiving propafenone.[1] In another patient peripheral neuropathy developed 10 months after starting treatment but symptoms had resolved 6 months after stopping the drug.[2] There have also been reports of ataxia.[3]

1. Chua TP, *et al.* Myoclonus associated with propafenone. *BMJ* 1994; **308:** 113.
2. Galasso PJ, *et al.* Propafenone-induced peripheral neuropathy. *Mayo Clin Proc* 1995; **70:** 469–72.
3. Odeh M, *et al.* Propafenone-induced ataxia: report of three cases. *Am J Med Sci* 2000; **320:** 151–3.

Lupus erythematosus. Symptoms of lupus erythematosus and raised antinuclear antibody titres were associated with propafenone therapy on 2 occasions in a 63-year-old woman.[1]

1. Guindo J, *et al.* Propafenone and a syndrome of the lupus erythematosus type. *Ann Intern Med* 1986; **104:** 589.

Precautions

Propafenone is contra-indicated in patients with uncontrolled heart failure, conduction disturbances including heart block unless controlled by artificial pacing, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, or pronounced hypotension. It may alter the endocardial pacing threshold and adjustment may be necessary in patients with pacemakers.

Propafenone has beta-blocking activity and may exacerbate obstructive airways disease; it should be used with great caution in such disorders and is contra-indicated in severe disease. Propafenone may aggravate myasthenia gravis and should be avoided in patients with this condition. Electrolyte disturbances should be corrected before beginning treatment. Propafenone should be used with caution in patients with hepatic or renal impairment.

Pregnancy and breast feeding. Experience in a patient given propafenone throughout the last trimester of pregnancy indicated that despite transplacental diffusion propafenone could safely be used at this time without harm to the fetus. Propafenone and its metabolite were detected in breast milk at concentrations considered to represent a markedly subtherapeutic dose to an infant.[1]

1. Libardoni M, *et al.* Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol* 1991; **32:** 527–8.

Interactions

Propafenone is extensively metabolised by the cytochrome P450 enzyme system, mainly by the isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Interactions may therefore occur with other drugs that are metabolised by these enzymes. Plasma-propafenone concentrations may be reduced by enzyme inducers such as rifampicin; enzyme inhibitors, such as cimetidine, fluoxetine, quinidine, and HIV-protease inhibitors, may increase plasma-propafenone concentrations. Propafenone itself may alter the plasma concentrations of other drugs, including beta blockers, ciclosporin, desipramine, digoxin, theophylline, venlafaxine, and warfarin. The absorption of propafenone may be reduced by orlistat. There may be an increased risk of arrhythmias if propafenone is given with other antiarrhythmics or arrhythmogenic drugs.

Antiarrhythmics. *Quinidine* inhibits the hepatic metabolism of propafenone and has been reported[1] to increase plasma-propafenone concentrations in extensive metabolisers;[1] the plasma concentration of the active 5-hydroxy metabolite was reduced and that of the *N*-depropyl metabolite increased but there was no change in the clinical response. Another study,[2] however, found that quinidine increased the beta-blocking effect of propafenone in extensive metabolisers, and a study[3] in patients with refractory atrial fibrillation found that addition of quinidine to propafenone was as effective and possibly better tolerated than increasing the propafenone dose.

1. Funck-Brentano C, *et al.* Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 1989; **27:** 435–44.
2. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* 1994; **55:** 28–34.
3. Lau C-P, *et al.* Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 2000; **86:** 1327–32.

Antibacterials. *Rifampicin* has lowered steady-state plasma concentrations of propafenone with the reappearance of arrhythmia.[1]

1. Castel JM, *et al.* Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* 1990; **30:** 155–6.

Histamine H_2-antagonists. *Cimetidine* has been reported[1] to raise plasma-propafenone concentrations. The mean steady-state concentration increased by 22% but the wide interindividual variability meant this change was not significant.

1. Pritchett ELC, *et al.* Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* 1988; **28:** 619–24.

Pharmacokinetics

Propafenone is readily and almost completely absorbed from the gastrointestinal tract. It is metabolised in the liver, largely by the cytochrome P450 isoenzyme CYP2D6, but also to a small extent by CYP1A2 and CYP3A4; the extent of metabolism is genetically determined. In subjects with the extensive metaboliser phenotype there is extensive first-pass metabolism to two active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone, and to other minor inactive metabolites. In the small proportion of subjects with the slow metaboliser phenotype (lacking CYP2D6) little or no 5-hydroxypropafenone is formed. The bioavailability of propafenone is dependent upon metaboliser phenotype but more importantly on dosage as the first-pass metabolism is saturable. In practice doses are high enough to compensate for differences in phenotype. Propafenone and its metabolites also undergo glucuronidation.

Propafenone is more than 95% protein bound.

Propafenone is excreted in the urine and faeces mainly in the form of conjugated metabolites. The elimination half-life is reported to be 2 to 10 hours in extensive metabolisers and 10 to 32 hours in slow metabolisers.

Propafenone crosses the placenta and is distributed into breast milk.

◊ General references.

1. Hii JTY, *et al.* Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; **21:** 1–10.

Uses and Administration

Propafenone is a class Ic antiarrhythmic (p.1153) with some negative inotropic and beta-adrenoceptor blocking activity. It is used in the management of supraventricular and ventricular arrhythmias.

Treatment should be started under close monitoring of the ECG and blood pressure. The usual initial oral dose of propafenone hydrochloride is 150 mg three times daily and this may be increased, if necessary, at intervals of 3 to 4 days up to a maximum of 300 mg three times daily. Reduced doses may be appropriate in patients weighing less than 70 kg and in the elderly; dose reduction may also be necessary in hepatic impairment (see below).

Propafenone hydrochloride is available in some countries as a modified-release preparation. It has also been given by slow intravenous injection or by infusion.

Administration in hepatic impairment. The clearance of propafenone may be reduced in hepatic impairment; careful monitoring is required and lower doses should be considered. US licensed product information states that the dose should be only 20 to 30% of that given in normal hepatic function.

Administration in renal impairment. A study[1] of the disposition of propafenone found that renal function did not affect the pharmacokinetics of propafenone or 5-hydroxypropafenone, and another study[2] suggested that propafenone could be used safely for atrial fibrillation in patients with chronic renal failure. Nevertheless, UK and US licensed product information states that caution is necessary if propafenone is given to patients with renal impairment.

Propafenone does not appear to be removed by haemofiltration.[3]

1. Fromm MF, *et al.* Influence of renal function on the steady-state pharmacokinetics of the antiarrhythmic propafenone and its phase I and phase II metabolites. *Eur J Clin Pharmacol* 1995; **48:** 279–83.
2. Napoli C, *et al.* Propafenone in the conversion of atrial fibrillation in patients suffering from chronic renal failure. *Am J Ther* 1997; **4:** 130–3.
3. Seto W, *et al.* Propafenone disposition during continuous venovenous hemofiltration. *Ann Pharmacother* 1999; **33:** 957–9.

Cardiac arrhythmias. Propafenone is effective in many cardiac arrhythmias.[1,2] It may have a role in the management of supraventricular arrhythmias (see p.1160), including as a single oral loading dose for recent-onset atrial fibrillation.[3,4] It may also be used in ventricular arrhythmias, although in many cases non-pharmacological therapy is preferred. Successful use in children with various arrhythmias has also been reported.[5,6]

1. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias: a risk-benefit appraisal. *Drug Safety* 1995; **12:** 55–72.
2. Reimold SC, *et al.* Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. *Am J Cardiol* 1998; **82:** 66N–71N.
3. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001; **37:** 542–7.
4. Boriani G, *et al.* Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. *Drugs* 2002; **62:** 415–23.
5. Heusch A, *et al.* Clinical experience with propafenone for cardiac arrhythmias in the young. *Eur Heart J* 1994; **15:** 1050–6.
6. Janoušek J, Paul T. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European Retrospective Multicenter Study). *Am J Cardiol* 1998; **81:** 1121–4.

Preparations

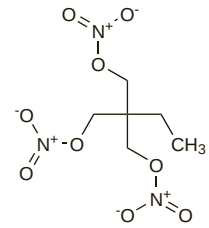
Proprietary Preparations (details are given in Part 3)
Arg.: Normorytmin; ***Austria:*** Asonacor†; Rhythmocor; Rytmonorma; ***Belg.:*** Rytmonorm; ***Braz.:*** Ritmonorm; ***Canad.:*** Rythmol; ***Chile:*** Ritmocor; Rytmonorm†; ***Cz.:*** Prolekofen; Propa-Tabletten†; Propanorm; Rytmonorm; ***Denm.:*** Rytmonorm; ***Fin.:*** Rytmonorm; ***Fr.:*** Rythmol; ***Ger.:*** Cuxafenon; Jutanorm†; Propamerck†; Rytmo-Puren; Rytmogenat†; Rytmonorm; ***Gr.:*** Rythmonorm; ***Hong Kong:*** Rytmonorm; ***Hung.:*** Rytmonorm; ***Indon.:*** Rytmonorm; ***Irl.:*** Arythmol; ***Israel:*** Profex; Rythmex; ***Ital.:*** Cardiofenone; Fenorit; Rytmonorm; ***Malaysia:*** Rytmonorm†; ***Mex.:*** Biopafen; Homopafen†; Nistaken; Norfenon; ***Neth.:*** Rytmonorm; ***NZ:*** Rytmonorm; ***Philipp.:*** Rytmocard; ***Pol.:*** Polfenon; Rytmonorm; ***Port.:*** Arythmol; Rytmonorm; ***Rus.:*** Propanorm (Пропанорм); Rytmonorm (Ритмонорм); ***S.Afr.:*** Rythmol; ***Singapore:*** Rytmonorm; ***Spain:*** Rytmonorm; ***Swed.:*** Rytmonorm; ***Switz.:*** Rytmonorm; ***Thai.:*** Rytmonorm; ***Turk.:*** Rytmonorm; ***UK:*** Arythmol; ***USA:*** Rythmol; ***Venez.:*** Rytmonorm.

Propatylnitrate *(BAN, rINN)*

ETTN; Ettriol Trinitrate; Propatilnitrato; Propatyl Nitrate *(USAN)*; Propatylnitrat; Propatylnitratum; Propatyylinitraatti; Trinettriol; Win-9317. 2-Ethyl-2-hydroxymethylpropane-1,3-diol trinitrate.

Пропатилнитрат

$C_6H_{11}N_3O_9$ = 269.2.
CAS — 2921-92-8.
ATC — C01DA07.
ATC Vet — QC01DA07.



Profile

Propatylnitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) that has been used in angina pectoris.

Preparations

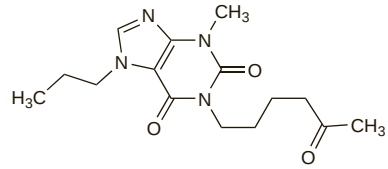
Proprietary Preparations (details are given in Part 3)
Braz.: Sustrate.

Propentofylline *(BAN, rINN)*

HWA-285; Propentofilina; Propentofylliini; Propentofyllin; Propentofyllinum. 3-Methyl-1-(5-oxohexyl)-7-propylxanthine.

Пропентофиллин

$C_{15}H_{22}N_4O_3$ = 306.4.
CAS — 55242-55-2.
ATC — N06BC02.
ATC Vet — QC04AD90; QN06BC02; QR03DA90.



Profile

Propentofylline is a xanthine derivative that has been investigated in cerebrovascular disorders including dementia. It is also used in veterinary medicine.

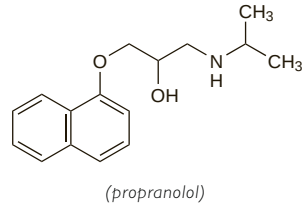
Propranolol Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-64043; Hidrocloruro de propranolol; ICI-45520; NSC-91523; Propanolol-hidroklorid; Propanololi Hydrochloridum; Propranolol, chlorhydrate de; Propranolol Hidroklorür; Propranolol-hydrochlorid; Propranololhydroklorid; Propranololi hydrochloridum; Propranololihydrokloridi; Propranololio hidrochloridas; Propranololu chlorowodorek. (±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride.

Пропранолола Гидрохлорид

$C_{16}H_{21}NO_2$,HCl = 295.8.
CAS — 525-66-6 (propranolol); 13013-17-7 (propranolol); 318-98-9 (propranolol hydrochloride); 3506-09-0 (propranolol hydrochloride).
ATC — C07AA05.
ATC Vet — QC07AA05.



(propranolol)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Propranolol Hydrochloride). A white or almost white powder. Soluble in water and in alcohol.
USP 31 (Propranolol Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. In aqueous solutions propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a