with moderate or severe renal impairment (creatinine clearance less than 20 mL/minute). Doses may need to be reduced in patients with heart failure or after myocardial infarction if renal function deteriorates.

Preparations

USP 31: Valsartan and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alpertan; Diovan; Redutensil†; Sarval; Simultan; ***Austria:*** Angiosan; Diovan; ***Belg.:*** Diovane; ***Braz.:*** Diovan; Tareg†; ***Canad.:*** Diovan; ***Chile:*** Tareg; Valaplex; Vartalan; ***Cz.:*** Diovan; Sarton†; Valsacor; ***Denm.:*** Diovan; ***Fin.:*** Diovan; ***Fr.:*** Nisis; Tareg; ***Ger.:*** Cordinate; Diovan; Provas; ***Gr.:*** Dalzad; Diovan; ***Hong Kong:*** Diovan; ***Hung.:*** Diovan; Varexan; ***India:*** Diovan; Starval; ***Indon.:*** Diovan; ***Irl.:*** Diovan; ***Israel:*** Diovan; ***Ital.:*** Rixil; Tareg; Valpression; ***Jpn:*** Diovan; ***Malaysia:*** Diovan; ***Mex.:*** Diovan; ***Neth.:*** Diovan; ***Norw.:*** Diovan; ***Philipp.:*** Diovan; ***Pol.:*** Diovan; ***Port.:*** Diovan; Tareg; ***Rus.:*** Diovan (Диован); ***S.Afr.:*** Diovan; Tareg; ***Singapore:*** Diovan; ***Spain:*** Diovan; Kalpress; Miten; Vals; ***Swed.:*** Diovan; ***Switz.:*** Diovan; Provas; ***Thai.:*** Diovan; ***Turk.:*** Diovan; ***UK:*** Diovan; ***USA:*** Diovan; ***Venez.:*** Alsart; Diovan; Vasaten.

Multi-ingredient: ***Arg.:*** Diovan A; Diovan D; Diovan Triple; Simultan D; ***Austria:*** Co-Angiosan; Co-Diovan; Valsartan/HCTZ†; ***Belg.:*** Co-Diovane; ***Braz.:*** Cotareg†; Diocomb Sl; Diovan Amlo; Diovan HCT; ***Canad.:*** Diovan HCT; ***Chile:*** Tareg-D; Valaplex-D; Vartalan D; ***Cz.:*** Co-Diovan; Copalia; Dafiro; Exforge; Imprida; ***Denm.:*** Diovan Comp; ***Fin.:*** Diovan Comp; ***Fr.:*** Cotareg; Nisisco; ***Ger.:*** Co-Diovan; Cordinate plus; Provas comp; ***Gr.:*** Co-Dalzad; Co-Diovan; Copalia; Dafiro; Exforge; ***Hong Kong:*** Co-Diovan; ***Hung.:*** Diovan HCT; Varexan HCT; ***Indon.:*** Co-Diovan; ***Irl.:*** Co-Diovan; ***Israel:*** Co-Diovan; ***Ital.:*** Combisartan; Corixil; Cotareg; ***Malaysia:*** Co-Diovan; ***Mex.:*** Co-Diovan; ***Neth.:*** Co-Diovan; Cotareg; ***Norw.:*** Diovan Comp; ***Philipp.:*** Co-Diovan; ***Pol.:*** Co-Diovan; ***Port.:*** Co-Diovan; Co-Tareg; Copalia; Dafiro; Imprida; ***Rus.:*** Co-Diovan (Ко-Диован); ***S.Afr.:*** Co-Diovan; ***Singapore:*** Co-Diovan; ***Spain:*** Co-Diovan; Co-Vals; Kalpress Plus; Miten Plus; ***Swed.:*** Diovan Comp; ***Switz.:*** Co-Diovan; Provas comp; Provas maxx; ***Thai.:*** Co-Diovan; ***Turk.:*** Co-Diovan; ***UK:*** Co-Diovan; Exforge; ***USA:*** Diovan HCT; Exforge; ***Venez.:*** Diovan HCT; Diovan/Amlibon; Vasaten HCT.

Verapamil Hydrochloride

(BANM, USAN, rINNM)

CP-16533-1 (verapamil); D-365 (verapamil); Hidrocloruro de verapamilo; Iproveratril Hydrochloride; Verapamiilihydrokloridi; Vérapamil, chlorhydrate de; Verapamil Hidroklorür; Verapamil-hidroklorid; Verapamil-hydrochlorid; Verapamilhydroklorid; Verapamili hydrochloridum; Verapamilio hidrochloridas. 5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

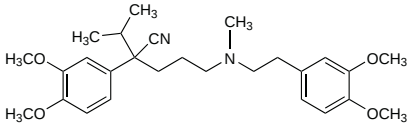
Верапамила Гидрохлорид

$C_{27}H_{38}N_2O_4,HCl = 491.1$.

CAS — 52-53-9 (verapamil); 152-11-4 (verapamil hydrochloride).

ATC — C08DA01.

ATC Vet — QC08DA01.



(verapamil)

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

Ph. Eur. 6.2 (Verapamil Hydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Verapamil Hydrochloride). A white or practically white, practically odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Verapamil hydrochloride will precipitate in alkaline solutions. There have been reports of incompatibility with solutions of aminophylline,[1] nafcillin sodium,[2] and sodium bicarbonate.[3]

1. Johnson CE, *et al.* Compatibility of aminophylline and verapamil in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 97–100.
2. Tucker R, Gentile JF. Precipitation of verapamil in an intravenous line. *Ann Intern Med* 1984; **101:** 880.
3. Cutie MR. Verapamil precipitation. *Ann Intern Med* 1983; **98:** 672.

Adverse Effects

Treatment with verapamil is generally well tolerated, but adverse effects connected with its pharmacological effects on cardiac conduction can arise and may be particularly severe in patients with previous myocardial damage or hypertrophic cardiomyopathies. Adverse effects on the heart include bradycardia, AV block, worsening heart failure, and transient asystole. These effects are more common with parenteral than with oral therapy.

The most troublesome non-cardiac adverse effect is constipation. Nausea may occur but is less frequently reported. Other adverse effects include hypotension, dizziness, flushing, headaches, fatigue, dyspnoea, and peripheral oedema. There have been reports of skin reactions and some cases of abnormal liver function and hepatotoxicity. Gingival hyperplasia has occurred. Gynaecomastia has been reported rarely.

In overdosage there may be severe cardiotoxicity and profound hypotension.

Carcinogenicity. See under Adverse Effects of Nifedipine, p.1350.

Effects on the cardiovascular system. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see Effects on Mortality, under Adverse Effects of Nifedipine, p.1350.

Verapamil has vasodilating properties and negative inotropic activity and may cause adverse cardiovascular effects with worsening of arrhythmias. As discussed under Precautions (below) certain cardiac disorders put the patient at risk of severe toxicity.

Some references.

1. Radford D. Side effects of verapamil in infants. *Arch Dis Child* 1983; **58:** 465–6.
2. Perrot B, *et al.* Verapamil: a cause of sudden death in a patient with hypertrophic cardiomyopathy. *Br Heart J* 1984; **51:** 352–4.
3. Kirk CR, *et al.* Cardiovascular collapse after verapamil in supraventricular tachycardia. *Arch Dis Child* 1987; **62:** 1265–6.
4. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure. *JAMA* 1989; **261:** 994.
5. Garratt C, *et al.* Degeneration of junctional tachycardia to pre-excited atrial fibrillation after intravenous verapamil. *Lancet* 1989; **ii:** 219.
6. Stajer D, *et al.* Cardiogenic shock following a single therapeutic oral dose of verapamil. *Int J Clin Pract* 2001; **55:** 69–70.
7. Shiraishi H, *et al.* Two cases of polymorphic ventricular tachycardia induced by the administration of verapamil against paroxysmal supraventricular tachycardia. *Intern Med* 2002; **41:** 445–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the endocrine system. Hyperprolactinaemia has been reported[1-4] in patients receiving verapamil, and in a few cases[2,3] patients have also had galactorrhoea.

Hyperglycaemia, metabolic acidosis, hyperkalaemia, and bradycardia have occurred[5] after a single dose of modified-release verapamil in a non-diabetic patient who had previously tolerated regular verapamil.

Verapamil has been reported not to affect the release of calcitonin,[6] thyroxine, tri-iodothyronine, thyrotrophin (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), or testosterone when given orally;[1] however, intravenous use has been reported to have an inhibitory effect on the release of FSH, LH, and TSH.[7]

1. Semple CG, *et al.* Calcium antagonists and endocrine status: lack of effect of oral verapamil on pituitary-testicular and pituitary-thyroid function. *Br J Clin Pharmacol* 1984; **17:** 179–82.
2. Gluskin LE, *et al.* Verapamil-induced hyperprolactinemia and galactorrhea. *Ann Intern Med* 1981; **95:** 66–7.
3. Fearrington EL, *et al.* Hyperprolactinemia-galactorrhea induced by verapamil. *Am J Cardiol* 1983; **51:** 1466–7.
4. Romeo JH, *et al.* Hyperprolactinaemia and verapamil: prevalence and potential association with hypogonadism in men. *Clin Endocrinol (Oxf)* 1996; **45:** 571–5.
5. Roth A, *et al.* Slow-release verapamil and hyperglycemic metabolic acidosis. *Ann Intern Med* 1989; **110:** 171–2.
6. Amado JA, *et al.* No effect of verapamil on calcium stimulated calcitonin release. *Postgrad Med J* 1987; **63:** 23–4.
7. Barbarino A, De Marinis L. Calcium antagonists and hormone release II: effects of verapamil on basal, gonadotrophin-releasing hormone- and thyrotrophin-releasing hormone-induced pituitary hormone release in normal subjects. *J Clin Endocrinol Metab* 1980; **51:** 749–53.

Effects on the gastrointestinal tract. For a report of intestinal pseudo-obstruction related to verapamil use, see under Adverse Effects of Diltiazem, p.1265.

Effects on the liver. Elevated serum concentrations of liver enzymes and bilirubin have been reported during verapamil therapy.[1-5] Clinical symptoms of hepatotoxicity such as abdominal pain, fever, darkened urine, and malaise have also occurred.[2-5] These reactions might have been due to a hypersensitivity reaction and were reversible on stopping verapamil.

1. Brodsky SJ, *et al.* Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981; **94:** 490–1.
2. Stern EH, *et al.* Possible hepatitis from verapamil. *N Engl J Med* 1982; **306:** 612–13.
3. Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983; **249:** 395–6.
4. Guarascio P, *et al.* Liver damage from verapamil. *BMJ* 1984; **288:** 362–3.
5. Kumar KL, Colley CA. Verapamil-induced hepatotoxicity. *West J Med* 1994; **160:** 485–6.

Effects on the mouth. Gingival hyperplasia[1] and oral mucosal injury[2] have been associated with verapamil therapy. A study involving 115 patients who had received nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[3]

1. Pernu HE, *et al.* Verapamil-induced gingival overgrowth: a clinical, histologic, and biochemic approach. *J Oral Pathol Med* 1989; **18:** 422–5.
2. Guttenberg SA. Chemical injury of the oral mucosa from verapamil. *N Engl J Med* 1990; **323:** 615.
3. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the nervous system. There has been a report[1] of 3 patients who complained of unusual perceptual symptoms, described as painful coldness and numbness or bursting feelings, especially in the legs, while taking oral verapamil.

1. Kumana CR, Mahon WA. Bizarre perceptual disorder of extremities in patients taking verapamil. *Lancet* 1981; **i:** 1324–5.

Effects on the neuromuscular system. Movement disorders, including acute dystonia,[1] myoclonic dystonia,[2] myoclonus,[3,4] and parkinsonism,[5,6] have occurred in patients receiving verapamil. However, there have also been reports of the successful use of verapamil in refractory movement disorders (see below).

1. Pina MA, *et al.* Verapamil and acute dystonia. *J Clin Pharm Ther* 1998; **23:** 79–80.
2. Hicks CB, Abraham K. Verapamil and myoclonic dystonia. *Ann Intern Med* 1985; **103:** 154.
3. Maiteh M, Daoud AS. Myoclonic seizure following intravenous verapamil injection: case report and review of the literature. *Ann Trop Paediatr* 2001; **21:** 271–2.
4. Vadlamudi L, Wijdicks EFM. Multifocal myoclonus due to verapamil overdose. *Neurology* 2002; **58:** 984.
5. García-Albea E, *et al.* Parkinsonism unmasked by verapamil. *Clin Neuropharmacol* 1993; **16:** 263–5.
6. Padrell MD, *et al.* Verapamil-induced parkinsonism. *Am J Med* 1995; **99:** 436.

Effects on the peripheral circulation. Secondary erythermalgia, a vasospastic arterial disorder that may be caused by vasoactive drugs, has been reported[1,2] in patients taking verapamil. Symptoms included burning pain, swelling, and erythema of the hands[2] and feet,[1,2] and resolved when verapamil was stopped. Similar reactions have been reported with nifedipine and other calcium-channel blockers (see p.1351).

1. Drenth JPH, *et al.* Verapamil-induced secondary erythermalgia. *Br J Dermatol* 1992; **127:** 292–4.
2. Hart JJ. Painful, swollen, and erythematous hands and feet. *Arthritis Rheum* 1996; **39:** 1761–2.

Effects on the respiratory tract. A patient with a history of bronchial asthma developed symptoms of acute asthma after use of a modified-release verapamil preparation;[1] it was possible that excipients, notably alginate, may have been responsible for the reaction.

1. Ben-Noun L. Acute asthma associated with sustained-release verapamil. *Ann Pharmacother* 1997; **31:** 593–5.

Effects on sexual function. In a group of 14 men taking verapamil, 3 reported impotence;[1] in 1 patient normal sexual function returned when verapamil was stopped, but impotence recurred on rechallenge.

1. King BD, *et al.* Impotence during therapy with verapamil. *Arch Intern Med* 1983; **143:** 1248–9.

Effects on the skin and hair. The commonest skin reactions to verapamil have been rash, pruritus, alopecia, and urticaria;[1] there have been a few reports of erythema multiforme, the Stevens-Johnson syndrome, and exfoliative dermatitis.[1] Hypertrichosis, over many parts of the body, has been reported in a male patient within about 1 month of starting verapamil therapy.[2] In a female patient who had been prematurely grey for about 40 years use of verapamil caused portions of the hair to regrow in its original natural black colour.[3]

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Sever PS. Hypertrichosis and verapamil. *Lancet* 1991; **338:** 1215–16.
3. Read GM. Verapamil and hair colour change. *Lancet* 1991; **338:** 1520.

Haemorrhage. See Effects on the Blood under Adverse Effects of Nifedipine, p.1350.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p.1352, but see also below.

Verapamil is not removed by dialysis.

Overdosage. The consequences and treatment of overdosage with verapamil are similar to those with other calcium-channel blockers (see Treatment of Adverse Effects under Nifedipine, p.1352), although death and life-threatening complications may be more common with non-dihydropyridines such as verapamil; a number of fatalities have occurred.[1]

Individual reports of overdosage with verapamil have included:

- A patient[2] who took 3.2 g of verapamil developed bradycardia and hypotension, which responded to intravenous calcium gluconate injection. A continuous infusion of calcium gluconate was given for 12 hours to maintain sinus rhythm. The

blood-verapamil concentration measured 5 hours after ingestion was 4 micrograms/mL.

- A patient[3] presented with loss of consciousness, severe hypotension, and bradycardia up to 18 hours after taking at least 1.2 g of verapamil. Treatment with glucagon, prenalterol, and atropine was unsuccessful, and there was a minimal response to intravenous calcium gluconate. Dobutamine and isoprenaline were given to maintain the blood pressure and mechanical ventilation was required for 24 hours, during which time metabolic acidosis and hyperglycaemia developed. The patient survived with cerebral anoxic damage.
- A patient[4] who had taken an unknown amount of verapamil developed cyanosis, undetectable blood pressure, and complete heart block. There was some response to sympathomimetics and calcium gluconate, although pacing was necessary to reverse the bradycardia. However, hypotension unresponsive to sympathomimetics developed after an episode of asystole and the patient died 19 hours after admission. The serum-verapamil concentration 12 hours after admission was 3 micrograms/mL.
- Haematemesis occurred in a patient[5] who took 3.2 g of verapamil; gastric ulceration was found on gastroscopy 12 hours after admission.

Overdosage with modified-release preparations of verapamil may result in prolonged toxicity of delayed onset.[6] Conventional-release preparations may also produce prolonged toxicity; elimination half-life was reported to be prolonged to 15 hours and peak plasma concentrations delayed to 6 to 7 hours in a 59-year-old man after ingestion of 2.4 g of verapamil.[7] Rate-limiting absorption at high doses was considered to be the cause.

Although severe toxicity usually relates to acute verapamil overdosage, similar symptoms have also been reported with chronic toxicity. Long-term treatment with verapamil 240 mg daily[8] in a patient with cirrhosis of the liver led to loss of consciousness, cardiogenic shock, cyanosis, hypotension, severe acidosis, hyperkalaemia, hypothermia, and renal failure. The patient recovered after treatment with high doses of dopamine, noradrenaline, sodium bicarbonate, and sodium chloride.

1. Hofer CA, *et al.* Verapamil intoxication: a literature review of overdoses and discussions of therapeutic options. *Am J Med* 1993; **95:** 431–8.
2. Perkins CM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. *BMJ* 1978; **2:** 1127.
3. Crump BJ, *et al.* Lack of response to intravenous calcium in severe verapamil poisoning. *Lancet* 1982; **ii:** 939–40.
4. Orr GM, *et al.* Fatal verapamil overdose. *Lancet* 1982; **ii:** 1218–19.
5. Miller ARO, Ingamells CJ. Gastrointestinal haemorrhage associated with an overdose of verapamil. *BMJ* 1984; **288:** 1346.
6. Barrow PM, *et al.* Overdose of sustained-release verapamil. *Br J Anaesth* 1994; **72:** 361–5.
7. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. *Br J Clin Pharmacol* 1995; **39:** 680–3.
8. Stehle G, *et al.* Cardiogenic shock associated with verapamil in a patient with liver cirrhosis. *Lancet* 1990; **336:** 1079.

Precautions

Verapamil is contra-indicated in hypotension, cardiogenic shock, marked bradycardia, and uncompensated heart failure. It is also contra-indicated in second- or third-degree AV block, and in the sick-sinus syndrome, unless a pacemaker is fitted. There is an increased incidence of adverse cardiac effects in patients with hypertrophic cardiomyopathy. In patients with atrial flutter or fibrillation and an accessory pathway with anterograde conduction, for example Wolff-Parkinson-White syndrome, verapamil may induce severe ventricular tachycardia and it is usually contra-indicated in such patients.

Special care is required in using verapamil as an antiarrhythmic in infants as they may be more susceptible to verapamil-induced arrhythmias.

Doses of verapamil should be reduced in patients with hepatic impairment.

Sudden withdrawal of verapamil might be associated with exacerbation of angina.

Breast feeding. Verapamil concentrations in breast milk similar to those found in plasma have been reported[1] in a woman taking verapamil 80 mg four times daily. The maximum concentration measured in breast milk was 300 nanograms/mL. However, the average concentration in milk in another woman[2] taking 80 mg three times daily was 23% of that in serum. The serum concentration of verapamil in the breast-fed child was 2.1 nanograms/mL during treatment and undetectable 38 hours after the last maternal dose. In another patient[3] taking the same dose, the average steady-state concentrations of verapamil and norverapamil in milk were, respectively, 60% and 16% of the concentration in plasma, with the ratio between milk and plasma varying during a dosage interval. It was estimated that the infant received less than 0.01% of the mother's dose, and no verapamil or norverapamil could be detected in the plasma of the infant. No adverse effects have been seen in breast-feeding infants, and the American Academy of Pediatrics considers[4] that verapamil is therefore usually compatible with breast feeding.

1. Inoue H, *et al.* Level of verapamil in human milk. *Eur J Clin Pharmacol* 1984; **26:** 657–8.
2. Andersen HJ. Excretion of verapamil in human milk. *Eur J Clin Pharmacol* 1983; **25:** 279–80.
3. Anderson P, *et al.* Verapamil and norverapamil in plasma and breast milk during breast feeding. *Eur J Clin Pharmacol* 1987; **31:** 625–7.
4. 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 10/07/07)

Muscular disorders. Sudden respiratory failure was believed to have been precipitated by intravenous verapamil therapy in a patient with Duchenne's muscular dystrophy.[1]

1. Zalman F, *et al.* Acute respiratory failure following intravenous verapamil in Duchenne's muscular dystrophy. *Am Heart J* 1983; **105:** 510–11.

Porphyria. Verapamil has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Wolff-Parkinson-White Syndrome. Patients with atrial flutter or fibrillation and an accessory pathway, such as those with Wolff-Parkinson-White syndrome, may be at increased risk of developing ventricular tachycardia if AV-blocking drugs such as verapamil are used, since conduction across the anomalous pathway may be increased. Ventricular fibrillation and severe hypotension have been reported[1] after the use of intravenous verapamil 5 to 10 mg in patients with the Wolff-Parkinson-White syndrome.

1. McGovern B, *et al.* Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. *Ann Intern Med* 1986; **104:** 791–4.

Interactions

Verapamil should be used with caution with drugs that have antiarrhythmic or beta-blocking effects; the use of intravenous verapamil with a beta blocker is especially hazardous (see below). Verapamil is extensively metabolised in the liver and interactions may occur with drugs that inhibit or enhance hepatic metabolism. Grapefruit juice may cause increased plasma concentrations of verapamil. Verapamil can itself affect the pharmacokinetics of other drugs, particularly by inhibition of the cytochrome P450 isoenzyme CYP3A4 and by effects on P-glycoprotein. Drugs affected include carbamazepine, ciclosporin, digoxin, midazolam, simvastatin, and theophylline; the plasma concentration of alcohol may also be increased. For details of these interactions, see under the individual drug monographs.

Analgesics. For a possible interaction of verapamil with *aspirin*, see under Antiplatelets, below.

Antiarrhythmics. Verapamil may have pharmacodynamic and pharmacokinetic interactions with other antiarrhythmics. Cardiogenic shock and asystole occurred in 2 patients receiving *flecainide* when verapamil was added to their therapy.[1] Verapamil given intravenously has been reported to cause severe hypotension in patients also receiving oral *quinidine*;[2] both drugs block alpha-adrenoceptors and verapamil may also increase the plasma concentration of quinidine.

1. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Acute verapamil toxicity manifested by complete heart block has been reported in a patient after the use of *ceftriaxone* and *clindamycin*.[1] Displacement of verapamil from binding sites was postulated as the probable mechanism of action. *Rifampicin* is an enzyme-inducing drug and has been reported[2,3] to reduce plasma-verapamil concentrations. A verapamil dose of 1.92 g was required to control supraventricular tachycardia in a patient also taking rifampicin[3] and when rifampicin was withdrawn the plasma-verapamil concentration 9 days later was almost four times higher. A patient taking propranolol and verapamil developed symptomatic bradycardia a few days after starting treatment with *clarithromycin* and on another occasion after starting treatment with *erythromycin*.[4] Inhibition of verapamil metabolism by the antibacterials was proposed as the mechanism for the interaction. A further case of severe hypotension and bradycardia has also been reported[5] in a patient shortly after beginning therapy with clarithromycin and verapamil, and similar effects were seen[6] in a patient 2 days after starting *telithromycin*. A case of complete heart block has been reported[7] in a patient aged 79 taking verapamil, one week after erythromycin was added to her therapy, probably due to mutual inhibition of hepatic metabolism of both drugs.

1. Kishore K, *et al.* Acute verapamil toxicity in a patient with chronic toxicity: possible interaction with ceftriaxone and clindamycin. *Ann Pharmacother* 1993; **27:** 877–80.
2. Rahn KH, *et al.* Reduction of bioavailability of verapamil by rifampin. *N Engl J Med* 1985; **312:** 920–1.
3. Barbarash RA. Verapamil-rifampin interaction. *Drug Intell Clin Pharm* 1985; **19:** 559–60.
4. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* 1998; **32:** 387–8.
5. Kaeser YA, *et al.* Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health-Syst Pharm* 1998; **55:** 2417–18.
6. Reed M, *et al.* Verapamil toxicity resulting from a probable interaction with telithromycin. *Ann Pharmacother* 2005; **39:** 357–60.
7. Goldschmidt N, *et al.* Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* 2001; **35:** 1396–9.

Antiepileptics. *Phenobarbital* is a hepatic enzyme-inducing drug and has been reported[1] to increase the clearance of oral and intravenous verapamil and to reduce oral bioavailability in healthy subjects. Plasma protein binding of verapamil was also reduced. Dosage adjustment of verapamil may be needed in patients also taking phenobarbital. Marked reduction in verapamil concentrations has also occurred with *phenytoin*.[2]

For a report of neurotoxicity in patients given verapamil with *carbamazepine*, see Calcium-channel Blockers, under Interactions of Carbamazepine, p.475.

1. Rutledge DR, *et al.* Effects of chronic phenobarbital on verapamil disposition in humans. *J Pharmacol Exp Ther* 1988; **246:** 7–13.
2. Woodcock BG, *et al.* A reduction in verapamil concentrations with phenytoin. *N Engl J Med* 1991; **325:** 1179.

Antiplatelets. Calcium-channel blockers can inhibit platelet function (see Effects on the Blood under Adverse Effects of Nifedipine, p.1350). Use of verapamil and *aspirin* in an 85-year-old man was considered to be the cause of ecchymoses and retroperitoneal bleeding that developed about 3 weeks after starting treatment with the combination.[1]

1. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; **28:** 536–7.

Anxiolytics. For the effect of verapamil on plasma-*buspirone* concentrations, see p.966.

Benzodiazepines. For the effects of verapamil on the pharmacokinetics of *midazolam*, see Calcium-channel Blockers, p.990.

Beta blockers. Oral verapamil and beta blockers have been used together in the treatment of angina and hypertension but both drugs have cardiodepressant activity and the combination, if used at all, must be used with extreme caution; bradycardia, heart block, and left ventricular failure have been reported.[1-4] Bradycardia has also been reported[5] in a patient treated with *timolol* eye drops and oral verapamil. Patients with severe ischaemic heart disease or heart failure are particularly at risk.[6] The risks are increased with intravenous verapamil, and it has been suggested[6] that treatment with beta blockers should be stopped at least 24 hours before giving verapamil by this route; the interaction is particularly hazardous when both verapamil and beta blockers are given intravenously, and such combinations are not recommended.

Verapamil may also affect the pharmacokinetics of some beta blockers (see Calcium-channel Blockers, under Interactions of Beta Blockers, p.1229).

1. Eisenberg JNH, Oakley GDG. Probable adverse interaction between oral metoprolol and verapamil. *Postgrad Med J* 1984; **60:** 705–6.
2. Hutchison SJ, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 659–60.
3. Findlay IN, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1074.
4. McGourty JC, Silas JH. β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1624.
5. Pringle SD, MacEwen CJ. Severe bradycardia due to interaction of timolol eye drops and verapamil. *BMJ* 1987; **294:** 155–6.
6. McInnes GT. Interactions that matter: calcium blockers. *Prescribers' J* 1988; **28:** 60–4.

Calcium salts. Calcium salts antagonise the pharmacological response to verapamil and other calcium-channel blockers and are given intravenously to treat their adverse effects (see Treatment of Adverse Effects under Nifedipine, p.1352). Recurrence of atrial fibrillation has occurred[1] during maintenance verapamil treatment when calcium adipinate and calciferol were given orally.

1. Bar-Or D, Yoel G. Calcium and calciferol antagonise effect of verapamil in atrial fibrillation. *BMJ* 1981; **282:** 1585–6.

Everolimus. For the effect of verapamil on everolimus, see p.1834.

Histamine H_2-antagonists. Studies in healthy subjects using single doses of verapamil after pretreatment with *cimetidine* for up to 8 days have produced conflicting results. The pharmacokinetics of intravenous verapamil were unaltered by cimetidine in some studies,[1,2] but a 21% reduction in clearance and a 50% increase in the elimination half-life were also reported.[3] The pharmacokinetics of oral verapamil were unchanged in one study[2] but two others[1,4] reported a significant increase in bioavailability. Although one of these studies[1] found the interaction had no clinical effects, the other[4] reported an increased clinical effect in 5 of 6 subjects. The interaction with cimetidine appears to be stereoselective since the oral bioavailability of the *S*-enantiomer increased by 35% and that of the *R*-enantiomer by 15%.[4] The clin-

ical significance of this interaction in patients and during long-term verapamil treatment is unknown, but cimetidine should be used with caution in patients receiving verapamil.

1. Smith MS, *et al.* Influence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther* 1984; **36:** 551–4.
2. Abernethy DR, *et al.* Lack of interaction between verapamil and cimetidine. *Clin Pharmacol Ther* 1985; **38:** 342–9.
3. Loi C-M, *et al.* Effect of cimetidine on verapamil disposition. *Clin Pharmacol Ther* 1985; **37:** 654–7.
4. Mikus G, *et al.* Interaction of verapamil and cimetidine: stereochemical aspects of drug metabolism, drug disposition and drug action. *J Pharmacol Exp Ther* 1990; **253:** 1042–8.

Lithium. Verapamil may have effects on neuromuscular function (see under Adverse Effects, above) and neurotoxicity has occurred[1-4] in patients receiving lithium after the addition of verapamil to their therapy, despite serum-lithium concentrations (where reported[1,2,4]) remaining in the therapeutic range. Verapamil has also been reported to decrease serum-lithium concentrations.[5]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Price WA, Shalley JE. Lithium-verapamil toxicity in the elderly. *J Am Geriatr Soc* 1987; **35:** 177–8.
3. Helmuth D, *et al.* Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* 1989; **9:** 454–5.
4. Wright BA, Jarrett DB. Lithium and calcium channel blockers: possible neurotoxicity. *Biol Psychiatry* 1991; **30:** 635–6.
5. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.

St John's wort. A study in healthy subjects[1] found that repeated doses of St John's wort significantly reduced the plasma concentrations of both the *R*- and *S*-isomers of verapamil, probably due to induction of the cytochrome P450 isoenzyme CYP3A4.

1. Tannergren C, *et al.* St John's wort decreases the bioavailability of *R*- and *S*-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther* 2004; **75:** 298–309.

Theophylline. For the effects of verapamil on the pharmacokinetics of theophylline, see Calcium-channel Blockers, p.1144.

Pharmacokinetics

Verapamil is about 90% absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver and the bioavailability is only about 20%.

Verapamil exhibits bi- or tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hours after a single oral dose or after intravenous dosage. With repeated oral doses half-life increases to 4.5 to 12 hours. Verapamil acts within 5 minutes when given intravenously and within 1 to 2 hours when given orally; peak plasma concentrations occur 1 to 2 hours after an oral dose. There is considerable interindividual variation in plasma concentrations.

Verapamil is about 90% bound to plasma proteins. It is extensively metabolised in the liver to at least 12 metabolites of which norverapamil has been shown to have some activity. About 70% of a dose is excreted by the kidneys in the form of its metabolites but about 16% is excreted in the bile into the faeces. Less than 4% is excreted unchanged. Verapamil crosses the placenta and is distributed into breast milk.

◊ Reviews.

1. Hamann SR, *et al*. Clinical pharmacokinetics of verapamil. *Clin Pharmacokinet* 1984; **9:** 26–41.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.
3. Kang D, *et al.* Population analyses of sustained-release verapamil in patients: effects of sex, race, and smoking. *Clin Pharmacol Ther* 2003; **73:** 31–40.

The elderly. Studies[1-3] comparing the pharmacokinetics and pharmacodynamics of verapamil in elderly (61 years and older) and young subjects have found that clearance and elimination half-life are increased in older subjects, and increased plasma concentrations have also been reported. However, there may also be changes in the response to verapamil in older subjects that are not directly related to the plasma concentration.

1. Abernethy DR, *et al*. Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: altered electrocardiographic and hypotensive responses. *Ann Intern Med* 1986; **105:** 329–36.
2. Gupta SK, *et al.* Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *Br J Clin Pharmacol* 1995; **40:** 325–31.
3. Abernethy DR, *et al.* Verapamil metabolite exposure in older and younger men during steady-state oral verapamil administration. *Drug Metab Dispos* 2000; **28:** 760–5.

Metabolism. Verapamil is extensively metabolised in the liver to a number of metabolites, and several cytochrome P450 isoenzymes appear to be involved. An *in-vitro* study[1] has suggested that the main isoenzymes responsible for the metabolism of both enantiomers of verapamil are CYP3A4, CYP3A5, and CYP2C8, and that the same isoenzymes are involved in the further metabolism of norverapamil. However, since CYP2C8 generally makes up only a small part of the cytochrome P450 content of the liver, it was considered that this would have little significance for potential drug interactions. In contrast to some previous reports, the isoenzymes CYP1A2 and CYP2C9 were not found to be involved to any great extent.

1. Tracy TS, *et al.* Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. *Br J Clin Pharmacol* 1999; **47:** 545–52.

Stereospecificity. Verapamil is used as a racemic mixture. It has been shown[1] that *S*-verapamil is 3.3 times more potent than the racemic mixture and 11 times more potent than *R*-verapamil. Thus it was concluded that the cardiac effects of verapamil are related not to the total plasma-verapamil concentration but to the concentration of the *S*-isomer, and conventional plasma concentration monitoring will be of little value in establishing therapeutic plasma concentrations during multiple oral dosing.

A series of studies have been carried out to determine whether differences in the pharmacokinetics of the *R*- and *S*-isomers of verapamil could account for observed differences in the plasma concentration-response curve after oral and intravenous doses. When given intravenously, there were pronounced differences in the pharmacokinetics and protein binding of the 2 isomers;[2] the volume of distribution and total systemic clearance of *S*-verapamil were much higher than those of the *R*-isomer although the terminal half-life was similar. After oral doses of a mixture of *R*- and *S*-verapamil, plasma concentrations of the *R*-isomer were found to be substantially higher than those of the more potent *S*-isomer,[3] suggesting stereospecific first-pass hepatic metabolism and accounting for the apparent lower potency of verapamil when given orally. The proportion of *S*-isomer also depends on the oral formulation; modified-release formulations produce lower proportions of *S*-isomer in plasma than conventional formulations.[4]

1. Echizen H, *et al.* Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. *Clin Pharmacol Ther* 1985; **38:** 71–6.
2. Eichelbaum M, *et al.* Pharmacokinetics of (+)-, (−)- and (±)-verapamil after intravenous administration. *Br J Clin Pharmacol* 1984; **17:** 453–8.
3. Vogelgesang B, *et al.* Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of - and - verapamil examined with a stable isotope technique. *Br J Clin Pharmacol* 1984; **18:** 733–40.
4. Karim A, Piergies A. Verapamil stereoisomerism: enantiomeric ratios in plasma dependent on peak concentrations, oral input rate, or both. *Clin Pharmacol Ther* 1995; **58:** 174–84.

Uses and Administration

Verapamil is a phenylalkylamine calcium-channel blocker (p.1154) and a class IV antiarrhythmic (p.1153). It slows conduction through the AV node, and thus slows the increased ventricular response rate that occurs in atrial fibrillation and flutter. Its anti-anginal effect is mainly due to coronary and peripheral vasodilatation, although it also inhibits coronary artery spasm; the decrease in peripheral vascular resistance reduces the work of the heart, which has a sparing effect on myocardial intracellular oxygen consumption. The decrease in peripheral vascular resistance may also explain its antihypertensive effect. Verapamil is used in the control of supraventricular arrhythmias and in the management of angina pectoris and hypertension. It may also be used in the management of myocardial infarction.

Verapamil may be given intravenously or orally, as the hydrochloride; doses are expressed in terms of verapamil hydrochloride.

In the acute management of supraventricular **arrhythmias** it is given intravenously, preferably under continuous ECG and blood pressure monitoring. The initial dose is 5 to 10 mg by slow intravenous injection over 2 to 3 minutes. If necessary, licensed product information in the UK allows a second dose of 5 mg to be given 5 to 10 minutes after the first; in the USA, a second dose of 10 mg may be given after 30 minutes.

Oral doses for the treatment of supraventricular arrhythmias are 120 to 480 mg daily in 3 or 4 divided doses, according to the severity of the condition and the patient's response.

In the management of **angina pectoris,** the usual oral dose is 120 mg three times daily; some patients with angina of effort may respond to 80 mg three times daily, but this lower dose is not likely to be effective in angina at rest or Prinzmetal's variant angina. Modified-release preparations may be given in doses of up to 480 mg daily.

In **hypertension** the usual initial oral dose is 240 mg daily, in 2 or 3 divided doses, adjusted according to response; doses of up to 480 mg daily have been used. Modified-release preparations may be given in similar daily doses.

In the secondary prevention of **myocardial infarction**, verapamil hydrochloride is given as a modified-release oral preparation, started at least 1 week after acute infarction (in patients without heart failure), in a dose of 360 mg daily in divided doses.

Doses of verapamil should be reduced in patients with hepatic impairment (see below).

For doses of verapamil in children with supraventricular arrhythmias or hypertension, see below.

◊ General reviews.

1. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. *Drugs* 1996; **51:** 792–819.
2. Prisant LM. Verapamil revisited: a transition in novel drug delivery systems and outcomes. *Heart Dis* 2001; **3:** 55–62.

Administration in children. Verapamil may be used for the treatment of supraventricular arrhythmias and hypertension in children, although great care is needed, especially in infants (see Precautions, above).

Intravenous doses of verapamil hydrochloride for supraventricular arrhythmias are as follows:

- children up to 1 year of age, 100 to 200 micrograms/kg
- 1 to 15 years, 100 to 300 micrograms/kg (to a maximum dose of 5 mg)

The dose should be given over at least 2 minutes and may be repeated after 30 minutes if necessary; doses at the lower end of the range may be adequate and the injection should be stopped when a response has been obtained.

Oral doses for supraventricular arrhythmias or for hypertension are:

- children up to 2 years of age, 20 mg two or three times daily
- 2 years and over, 40 to 120 mg two or three times daily according to age and response

Administration in the elderly. For a discussion of the effects of increasing age on verapamil, see under Pharmacokinetics, above.

Administration in hepatic impairment. Verapamil is extensively metabolised in the liver and should be used with caution in hepatic impairment; US licensed product information recommends that oral doses for patients with severe hepatic impairment should be reduced to about one-third of the usual dose (see above).

In a study[1] of patients with liver cirrhosis steady-state plasma concentrations of verapamil were double those seen in patients with normal liver function after intravenous doses and 5 times the normal concentration when given orally. The elimination half-life was prolonged about fourfold after oral or intravenous doses, suggesting that steady-state plasma concentration will not be reached in patients with liver cirrhosis until about 56 hours after therapy has started.

1. Somogyi A, *et al*. Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J Clin Pharmacol* 1981; **12:** 51–60.

Administration in renal impairment. The pharmacokinetics and pharmacodynamic effects of verapamil are not significantly altered by renal impairment[1] and dosage adjustment is not considered to be necessary. The elimination of verapamil is not altered by haemodialysis,[1,2] haemofiltration,[2] or peritoneal dialysis[2] and no dosage supplement is required in patients undergoing these procedures.

1. Mooy J, *et al*. Pharmacokinetics of verapamil in patients with renal failure. *Eur J Clin Pharmacol* 1985; **28:** 405–10.
2. Beyerlein C, *et al.* Verapamil in antihypertensive treatment of patients on renal replacement therapy—clinical implications and pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39** (suppl 1): S35–S37.

Amaurosis fugax. For a report of the use of verapamil in patients with amaurosis fugax, see under Uses and Administration of Nifedipine, p.1354.

Bipolar disorder. Although lithium and valproate are the mainstays of therapy in bipolar disorder (p.372) many other drugs have been tried, including verapamil.[1] Beneficial responses to verapamil at doses up to 480 mg daily have been reported,[2-4] although a review[5] concluded that there is limited support for its use. Verapamil has also been used with lithium, but there may be an increased risk of neurotoxicity (see under Interactions, above).

1. Höschl C. Do calcium antagonists have a place in the treatment of mood disorders? *Drugs* 1991; **42:** 721–29.
2. Dubovsky SL, *et al.* Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res* 1986; **18:** 309–20.
3. Giannini AJ, *et al.* Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol* 1987; **27:** 980–2.

4. Wisner KL, *et al.* Verapamil treatment for women with bipolar disorder. *Biol Psychiatry* 2002; **51:** 745–52.
5. Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. *Bipolar Disord* 2000; **2:** 108–19.

Box jellyfish sting. Stings by the box jellyfish (*Chironex fleckeri*) (p.2220) can be fatal because of the effects of the venom on the cardiovascular and respiratory systems and on the kidneys. Studies in *rodents* have reported a beneficial effect of intravenous verapamil in the treatment of box jellyfish envenomation, and use in patients with serious box-jellyfish stings has been recommended.[1] However, it has also been suggested[2] that the lack of evidence for benefit and the potential for adverse effects means that use of verapamil should be limited to extreme cases only.

1. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; **153:** 363.
2. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; **178:** 34–7.

Cardiac arrhythmias. Verapamil has an established role in the management of supraventricular cardiac arrhythmias (p.1160). It is used for rate control in atrial fibrillation and flutter, and may also be used in paroxysmal supraventricular tachycardia. It has been successfully used with digoxin for transplacental therapy in fetal atrial flutter or supraventricular tachycardia,[1,2] although caution is necessary if it is used in infants since they may be particularly susceptible to its adverse effects (see Precautions, above).

1. Maxwell DJ, *et al.* Obstetric importance, diagnosis, and management of fetal tachycardias. *BMJ* 1988; **297:** 107–10.
2. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.

Cardiomyopathies. Verapamil has an established role as a negative inotrope in the management of patients with *hypertrophic cardiomyopathy*,[1,2] although it is usually reserved for patients in whom beta blockers either fail to control symptoms or are not tolerated. It may improve symptoms and exercise tolerance; although a crossover study[3] failed to show an improvement in exercise capacity with verapamil or the beta blocker nadolol, most patients preferred drug treatment to placebo and there was an apparent improvement in quality of life with verapamil. Verapamil may also be useful for rate control in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. However, there is no evidence that it reduces the incidence of sudden cardiac death, and serious adverse effects have been reported,[4] especially in patients with severe outflow obstruction. Patients with hypertrophic cardiomyopathy appear to be particularly susceptible to conduction disturbances associated with verapamil, and this may worsen hypotension and outflow obstruction.

Dilated cardiomyopathy is treated similarly to heart failure and calcium-channel blockers are not usually used, although some benefit has been reported with diltiazem (see p.1267).

For a discussion of the management of cardiomyopathies in general, see p.1163.

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; **287:** 1308–20.
2. Maron BJ, *et al.* American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; **42:** 1687–713. Also published in *Eur Heart J* 2003; **24:** 1965–91. Also available at: http://www.acc.org/qualityandscience/clinical/consensus/cardiomyopathy/index.pdf (accessed 14/08/08) and at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HCM-FT.pdf (accessed 14/08/08)
3. Gilligan DM, *et al.* A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993; **21:** 1672–9.
4. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circulation* 1981; **64:** 437–41.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p.1355), although studies with verapamil have suggested that it is less effective than the ACE inhibitor trandolapril in patients with non-diabetic renal disease,[1] and that it does not prevent the development of renal disease in type 2 diabetics.[2] There is some evidence that verapamil may reduce the nephrotoxicity associated with certain drugs, including ciclosporin (see Transplantation, below), and the aminoglycoside gentamicin.[3]

1. Hemmelder MH, *et al.* Antiproteinuric efficacy of verapamil in comparison to trandolapril in non-diabetic renal disease. *Nephrol Dial Transplant* 1999; **14:** 98–104.
2. Ruggenenti P, *et al.* for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; **351:** 1941–51.
3. Kazierad DJ, *et al.* The effect of verapamil on the nephrotoxic potential of gentamicin as measured by urinary enzyme excretion in healthy volunteers. *J Clin Pharmacol* 1995; **35:** 196–201.

Malignant neoplasms. Verapamil has been shown to reverse multidrug resistance to antineoplastics in cultured cells and in *animal* studies,[1] but studies in which verapamil was added to therapy for small cell lung cancer[2] or multiple myeloma[3] failed to show any benefit. See p.643 for a discussion of resistance to antineoplastics.

1. Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; **42:** 155–99.
2. Milroy R, *et al.* A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; **68:** 813–18.
3. Dalton WS, *et al.* A phase III randomized study of oral verapamil as a chemosensitizer to reverse drug resistance in patients with refractory myeloma: a Southwest Oncology Group Study. *Cancer* 1995; **75:** 815–20.

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including verapamil, in the management of migraine and cluster headache, see under Nifedipine, p.1355.

Movement disorders. Verapamil has been associated with the development of various movement disorders (see under Adverse Effects, above) but there have also been case reports[1,2] of its successful use in refractory movement disorders, including severe tardive dyskinesia. However, a systematic review[3] concluded that evidence for the use of verapamil or other calcium-channel blockers in tardive dyskinesia is limited and they are not generally recommended.

The usual management of tardive dyskinesia is discussed under the Adverse Effects of Chlorpromazine, p.971.

1. Abad V, Ovsiew F. Treatment of persistent myoclonic tardive dystonia with verapamil. *Br J Psychiatry* 1993; **162:** 554–6.
2. Ovsiew F, *et al.* Verapamil for severe hyperkinetic movement disorders. *Mov Disord* 1998; **13:** 341–4.
3. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/03/07).

Myocardial infarction. Calcium-channel blockers are not routinely used in either the acute or long-term treatment of myocardial infarction (p.1175), although some benefit has been reported with non-dihydropyridines. Diltiazem, started within 24 to 72 hours of the onset of infarction and continued for up to 14 days, has been reported to protect against re-infarction and refractory angina in patients recovering from acute non-Q-wave infarction.[1] A pilot study[2] of intravenous diltiazem as an adjunct to thrombolysis in acute myocardial infarction also suggested a reduction in recurrent ischaemia; diltiazem was given intravenously for 48 hours, beginning at the same time as the thrombolytic, then continued orally for 4 weeks. However, a study[3] with verapamil, started on admission to hospital, found no effect on mortality at 6 months, and there was a suggestion that very early use (within 6 hours of symptom onset) was detrimental. A later study[4] reported that early use of verapamil in patients receiving thrombolysis improved outcome at 90 days. Benefit has also been shown[5] with use of intracoronary verapamil to terminate post-reperfusion arrhythmias. For use of verapamil in patients receiving percutaneous coronary intervention see Reperfusion and Revascularisation Procedures, below.

Although they are not standard therapy, diltiazem and verapamil may be used for long-term management in selected patients without heart failure. In a study by the Multicenter Diltiazem Postinfarction Trial (MDPIT) research group,[6] diltiazem (target dose 240 mg daily) reduced 1-year mortality and re-infarction rates in patients without left ventricular dysfunction, but increased such adverse events in those with left ventricular dysfunction. Re-analysis of the study provided further evidence that diltiazem should be avoided in postinfarction patients with left ventricular dysfunction.[7] Another study[8] in patients with acute myocardial infarction treated with thrombolysis found no reduction in mortality with diltiazem started 36 to 96 hours after infarction and continued for up to 6 months, although the incidence of non-fatal cardiac events was reduced. Patients with heart failure were excluded from the trial. In the DAVIT II study[9] late intervention with verapamil (started in the second week after admission) reduced overall mortality, cardiac events, and re-infarction although another study[10] found only a benefit in re-infarction rate and not in overall mortality.

1. Gibson RS, *et al.* Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986; **315:** 423–9.
2. Théroux P, *et al.* Intravenous diltiazem in acute myocardial infarction: diltiazem as adjunctive therapy to activase (DATA) trial. *J Am Coll Cardiol* 1998; **32:** 620–8.
3. The Danish Study Group on Verapamil in Myocardial Infarction. The Danish studies on verapamil in acute myocardial infarction. *Br J Clin Pharmacol* 1986; **21:** 197S–204S.
4. Marangelli V, *et al.* Early administration of verapamil after thrombolysis in acute anterior myocardial infarction: effect on left ventricular remodeling and clinical outcome. *Ital Heart J* 2000; **1:** 336–43.
5. Kato M, *et al.* Intracoronary verapamil rapidly terminates reperfusion tachyarrhythmias in acute myocardial infarction. *Chest* 2004; **126:** 702–8.
6. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
7. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.
8. Boden WE, *et al.* Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. *Lancet* 2000; **355:** 1751–6.
9. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II–DAVIT II). *Am J Cardiol* 1990; **66:** 779–85.
10. Rengo F, *et al.* A controlled trial of verapamil in patients after acute myocardial infarction: results of the calcium antagonist reinfarction Italian study (CRIS). *Am J Cardiol* 1996; **77:** 365–9.

Peyronie's disease. Verapamil has been used by intraplaque injection for the treatment of Peyronie's disease.[1,2] Pain, curvature, and erectile dysfunction were all improved. A systematic review[2] of 19 studies involving plaque injection therapy for Peyronie's disease, of which 4 used verapamil, noted that although the results of these suggested that injection was safe and effective in mild to moderate Peyronie's disease, the quality of studies was generally poor and its efficacy needed to be verified. Verapamil has also been given by iontophoresis, but again benefits remain unclear. A study[3] comparing verapamil and dexamethasone with lidocaine reported considerable improvement in plaque volume, penile curvature, and pain in the group given verapamil and dexamethasone, while patients given lidocaine had a transient improvement in pain but no change in plaque volume or curvature. However, a study[4] comparing verapamil with sodium chloride as placebo reported some improvement with both treatments, with no difference between the groups.

1. Levine LA, *et al.* Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol (Baltimore)* 2002; **168:** 621–5.
2. Russell S, *et al.* Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol* 2007; **51:** 640–7.
3. Di Stasi SM, *et al.* A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol (Baltimore)* 2004; **171:** 1605–8.
4. Greenfield JM, *et al.* Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol (Baltimore)* 2007; **177:** 972–5.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention is widely used in the management of patients with acute myocardial infarction and angina pectoris, and adjunctive drug treatment has an important role in reducing complications and improving outcome (see p.1181). Intracoronary verapamil may be used to treat vasospasm[1] and has also been used to treat[2,3] and prevent[4,5] the 'no-reflow' phenomenon. However, transient heart block occurred in some patients given verapamil prophylactically,[5] and this may limit its use.

There is also some evidence that verapamil may reduce the incidence of restenosis after coronary[6] or peripheral[7] percutaneous interventions.

1. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005; **26:** 804–47. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf (accessed 14/08/08)
2. Piana RN, *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; **89:** 2514–18.
3. Demir I, *et al.* Treatment of no-reflow phenomenon with verapamil after primary stent deployment during myocardial infarction. *Jpn Heart J* 2002; **43:** 573–80.
4. Hang C-L, *et al.* Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest* 2005; **128:** 2593–8.
5. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
6. Bestehorn H-P, *et al.* Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: the randomized, double-blind, placebo-controlled, multicenter Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) Trial. *J Am Coll Cardiol* 2004; **43:** 2160–5.
7. Schweizer J, *et al.* Effect of high dose verapamil on restenosis after peripheral angioplasty. *J Am Coll Cardiol* 1998; **31:** 1299–1305.

Transplantation. Ciclosporin is widely used in transplantation to prevent rejection but its use is limited by its nephrotoxicity. Dihydropyridine calcium-channel blockers (see under Uses of Nifedipine, p.1356) and diltiazem (p.1267) have been reported to reduce ciclosporin-associated nephrotoxicity, and there is some evidence that verapamil may have a similar effect. Studies in renal[1,2] and heart or lung[3] transplant recipients suggested that verapamil can improve outcomes in patients receiving ciclosporin. Most studies have found that verapamil prevents ciclosporin-induced deterioration in renal function, despite increasing plasma-ciclosporin concentrations,[1,2] and there is also evidence[2] that graft survival may be improved. The beneficial effect of verapamil may be related to its ability to protect cells from ischaemia, selective vasodilatation of the afferent renal arterioles, or inherent immunosuppressive properties; its effect on plasma-ciclosporin concentrations may also be involved, either directly[1,2] or by allowing reduction of the ciclosporin dose.[3] However, one study[4] found that use of verapamil with ciclosporin resulted in higher serum-creatinine concentrations in patients given verapamil, with no reduction in the incidence of rejection, and careful monitoring is necessary if the drugs are used together. A higher incidence of severe infections has also

been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; **90** (suppl 5A): 37S–41S.
2. Dawidson I, *et al*. Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2:** 983–90.
3. Chan C, *et al*. A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; **63:** 1435–40.
4. Pirsch JD, *et al*. A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; **21:** 189–95.
5. Nanni G, *et al*. Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; **32:** 551–3.

Preparations

BP 2008: Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;
USP 31: Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Isoptino; Veral; Verapal†; ***Austral.:*** Anpec; Cordilox; Isoptin; Veracaps; Verahexal; ***Austria:*** Isoptin; Verapabene; Verastad; ***Belg.:*** Isoptine; Lodixal; ***Braz.:*** Cordilat; Coronaril; Cronovera†; Dilacard†; Dilacor; Dilacoron; Multicor; Neo Verpamil; Vascord†; Vasoton; Veramil; Veraval; ***Canad.:*** Apo-Verap; Chronovera; Isoptin; Novo-Veramil; Nu-Verap; ***Chile:*** Cardiolen; Isoptina; Presocor; ***Cz.:*** Apo-Verap†; Isoptin; Lekoptin; Verahexal; Verogalid; ***Denm.:*** Geangin; Hexasoptin; Isoptin; Veraloc; ***Fin.:*** Isoptin; Vermin; Verpamil; ***Fr.:*** Isoptine; ***Ger.:*** Azupamil†; durasoptin†; Falicard; Isoptin; Jenapamil†; Vera; Vera-Lich; Verabeta; Veragamma; Verahexal; Veramex; Veranorm; Verasal; Veroptinstada; ***Gr.:*** Brovicarpine†; Elanver†; Isoptin; ***Hong Kong:*** Akilen†; Isoptin; ***Hung.:*** Chinopamil; Isoptin; Verogalid†; ***India:*** Calaptin; Veramil; ***Indon.:*** Cardiover; Isoptin; ***Irl.:*** Isoptin; Veramil; Verap; Verisop; ***Israel:*** Apoacor; Ikacor; Ikapress; Veracor; Verapress; ***Ital.:*** Cardinorm; Isoptin; Kata†; Quasar†; Veraptin; ***Malaysia:*** Akilen; Anpec†; Cintsu†; Isoptin; Verpamil; Viratin†; ***Mex.:*** Cronovera; Dilacoran; Euritmin†; Europave; Serriten; Vepiltax; Veraken; Verdilac; ***Neth.:*** Chronovera†; Geangin; Isoptin; ***Norw.:*** Isoptin; Verakard; ***NZ:*** Civicor†; Isoptin; Verpamil; ***Philipp.:*** Isoptin; Verelan; ***Pol.:*** Isoptin; Lekoptin; Novo-Veramil; Staveran; ***Port.:*** Fibrocard; Isoptin; ***Rus.:*** Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин); Verogalid (Верогалид); ***S.Afr.:*** Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; ***Singapore:*** Isoptin; Verpamil; ***Spain:*** Manidon; ***Swed.:*** Isoptin; ***Switz.:*** Corpamil†; Flamon; Isoptin; Verapam; ***Thai.:*** Caveril; Civicor†; Isopamil†; Isoptin; Verapin; Vermine; ***Turk.:*** Fibrocard; Isoptin; Ormil; Veroptin; ***UK:*** Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; ***USA:*** Calan; Covera; Isoptin; Verelan; ***Venez.:*** Cronovera; Manidon; Veracor.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Captocomp; Confit; Tarka; Veracapt; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Cordichin; Isoptin plus; Stenoptin†; Tarka; Udramil†; Veratide; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

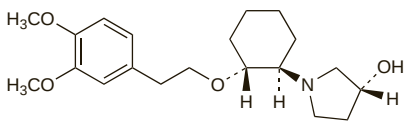
Vernakalant Hydrochloride *(USAN, rINNM)*

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum. (3*R*)-1-{(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl}pyrrolidin-3-ol hydrochloride.

Вернаканта Гидрохлорид

$C_{20}H_{31}NO_4$,HCl = 385.9.

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).



(vernakalant)

Profile

Vernakalant is an antiarrhythmic under investigation as the hydrochloride for the treatment of atrial arrhythmias.

◊ References.

1. Roy D, *et al*. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; **44:** 2355–61.
2. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Invest Drugs* 2007; **16:** 519–32.
3. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; **42:** 533–42.

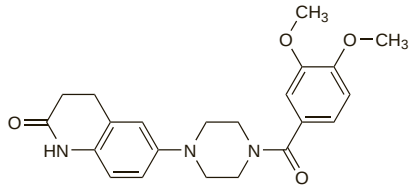
Vesnarinone *(USAN, rINN)*

OPC-8212; Vesnarinona; Vesnarinonum. 1-(1,2,3,4-Tetrahydro-2-oxo-6-quinolyl)-4-veratroylpiperazine.

Веснаринон

$C_{22}H_{25}N_3O_4$ = 395.5.

CAS — 81840-15-5.



Profile

Vesnarinone is a phosphodiesterase inhibitor with positive inotropic activity that has been tried orally in the management of heart failure.

Adverse effects. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate. In a multicentre study of vesnarinone,[1] doses of 120 mg daily resulted in increased mortality whereas 60 mg daily for 6 months was associated with lower morbidity and mortality. Reversible neutropenia occurred in 2.5% of the patients given 60 mg daily. However, in a subsequent larger study,[2] increased mortality was also reported with doses of 30 and 60 mg daily.

1. Feldman AM, *et al*. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993; **329:** 149–55.
2. Cohn JN, *et al*. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998; **339:** 1810–16.

Warfarin Sodium *(BANM, rINNM)*

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin sodná sůl; Warfarina sódica; Warfarine sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum. The sodium salt of 4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin ; Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate.

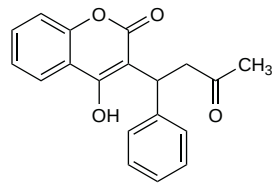
Натрий Варфарин

$C_{19}H_{15}NaO_4$ = 330.3.

CAS — 81-81-2 (warfarin); 2610-86-8 (warfarin potassium); 129-06-6 (warfarin sodium).

ATC — B01AA03.

ATC Vet — QB01AA03.



(warfarin)

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US*.
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).
Jpn includes Warfarin Potassium.
Ph. Eur. 6.2 (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
USP 31 (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] could demonstrate no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al*. Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Martens HJ, *et al*. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part i: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; **31:** 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al*. Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Warfarin Sodium Clathrate *(BANM)*

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum natricum clathratum. The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.

ATC — B01AA03.

ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p.vii).
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate.
Ph. Eur. 6.2 (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
Warfarin sodium clathrate contains about 92% of warfarin sodium.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied; one estimate is that if a coumarin anticoagulant is taken during pregnancy, one-sixth of pregnancies will result in an abnormal liveborn infant, and one-sixth will result in abortion or stillbirth.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical trials[1,2] and in population-based studies.[1,3-7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to