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

Urokinaasi; Urokinas; Urokinasa; Urokinasum; Ürokinaz; Urokináz; Urokinazė; Uroquinasa.

Урокиназа

*CAS — 9039-53-6.*
*ATC — B01AD04.*
*ATC Vet — QB01AD04.*

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

**Ph. Eur. 6.2** (Urokinase). An enzyme isolated from human urine that activates plasminogen. It consists of a mixture of low (33 000) and high (54 000) molecular mass forms, the high molecular mass form being predominant. The potency is not less than 70 000 international units per mg of protein. A white or almost white, amorphous powder. Soluble in water. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

**Stability.** Solutions of urokinase containing 2500 to 25 000 units/mL were found to be stable in single-use syringes when stored at –30° for 30 days and also when stored frozen for 7 days, thawed, and refrozen for a further 23 days.[1]

1. Dedrick SC, Ramirez-Rico J. Potency and stability of frozen urokinase solutions in syringes. *Am J Health-Syst Pharm* 2004; **61:** 1586–9.

### Units

The potency of urokinase is expressed in international units. Preparations are assayed using the first International Reference Preparation (1968), a mixture of low-molecular-weight and high-molecular-weight urokinases. The first International Standard for high-molecular-weight urokinase was established in 1989 for use with preparations of this type of urokinase.

Potency used to be expressed in Ploug or Plough units or in CTA units, but these now appear to be obsolete.

### Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Serious allergic reactions may be less likely to occur with urokinase than with streptokinase.

**Hypersensitivity.** Allergic reactions are considered to be less frequent with urokinase than with streptokinase. However, in a series of 6 patients who had previously been treated with streptokinase,[1] thrombolytic therapy with urokinase for recurrent myocardial infarction was associated with rigors in 4 patients, 2 of whom also developed bronchospasm. None of the patients had any history of atopy.

1. Matsis P, Mann S. Rigors and bronchospasm with urokinase after streptokinase. *Lancet* 1992; **340:** 1552.

**Transmission of infection.** Some preparations of urokinase are produced in cultures of human cells and there is a risk of transmission of infection associated with their use.

### Interactions

As for Streptokinase, p.1404.

### Pharmacokinetics

After intravenous infusion urokinase is cleared rapidly from the circulation by the liver. A plasma half-life of up to 20 minutes has been reported.

### Uses and Administration

Urokinase is a thrombolytic produced by the kidney and found in human urine. It directly converts plasminogen to plasmin, a proteolytic enzyme with fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Urokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p.1156).

Urokinase is used similarly to streptokinase (p.1404) in the management of thromboembolic disorders including venous thromboembolism (pulmonary embolism and deep-vein thrombosis; p.1189) and peripheral arterial thromboembolism (p.1178). It is also used to clear occluded catheters and cannulas. Urokinase has been used in myocardial infarction and for clearing clots after haemorrhage within the eye.

In the treatment of **venous thromboembolism**, urokinase is given by intravenous infusion in an initial dose of 4400 units/kg over 10 minutes. This is followed by 4400 units/kg per hour for 12 hours in pulmonary embolism, and for 12 to 24 hours in deep-vein thrombosis. Alternatively, patients with pulmonary embolism may be given a bolus injection of 15 000 units/kg into the pulmonary artery; the injection may be repeated, with the dose adjusted according to plasma-fibrinogen concentration, up to 3 times in 24 hours.

In the treatment of **peripheral arterial thromboembolism**, a solution containing urokinase 2000 units/mL is infused into the clot via a catheter at a rate of 4000 units/minute for 2 hours. Angiography should then be performed and, if flow has not resumed, the catheter should be advanced into the occluded vessel and the infusion continued at the same rate for a further 2 hours. The procedure may be repeated, if necessary, up to 4 times. Once blood flow is re-established, the catheter should be partially withdrawn and infusion continued at a rate of 1000 units/minute until the remaining clot has lysed; a dose of 500 000 units given over 8 hours is usually sufficient.

For **clearing occluded intravenous catheters or cannulas**, 5000 to 25 000 units of urokinase dissolved in 2 mL of sodium chloride 0.9% may be instilled into the device and clamped off for up to 4 hours; the lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5000 units of urokinase in 200 mL of sodium chloride 0.9% may be infused into the device over 30 minutes.

**Catheters and cannulas.** For reference to the use of urokinase to maintain patency of long-term venous access devices, see under Uses for Alteplase, p.1208.

### Preparations

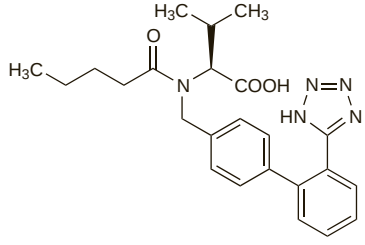
**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Abbokinase; Actosolv; ***Belg.:*** Actosolv; ***Cz.:*** Rheotromb; ***Ger.:*** Corase; Rheotromb; ***Gr.:*** Ukidan†; Urochinasi; ***Hung.:*** Rheotromb; ***India:*** Solokinase; Ukidan†; Uni-Kinase; ***Israel:*** Abbokinase; ***Ital.:*** Actosolv†; Alfakinasi†; Kisolv†; Persolv Richter†; ***Jpn:*** Uronase; ***Neth.:*** Medacinase; ***Port.:*** Ukidan†; ***Spain:*** Uroquidan; ***Swed.:*** Abbokinase†; ***UK:*** Syner-Kinase; ***USA:*** Abbokinase.

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

CGP-48933; Valsartaani; Valsartán; Valsartanum. *N*-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine; *N*-Pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine.

Вальзартан

$C_{24}H_{29}N_5O_3$ = 435.5.
*CAS — 137862-53-4.*
*ATC — C09CA03.*
*ATC Vet — QC09CA03.*



**Pharmacopoeias.** In *US.*

**USP 31** (Valsartan). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

**Suspension.** The US licensed product information provides the following method for making 160 mL of a suspension containing valsartan 4 mg/mL:

- add 80 mL of *Ora-Plus* (*Paddock, USA*) to an amber glass bottle containing eight 80-mg tablets (*Diovan, Novartis*) and shake for at least 2 minutes
- allow to stand for at least 1 hour then shake again for at least 1 minute
- add 80 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and shake for at least 10 seconds

The suspension can be stored for 30 days at or below 30° or for up to 75 days at 2° to 8°.

### Adverse Effects and Precautions

As for Losartan Potassium, p.1326. Valsartan should be used with caution in patients with hepatic impairment, cirrhosis, or biliary obstruction.

### Interactions

As for Losartan Potassium, p.1327.

### Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23%. Peak plasma concentrations of valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolised and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose about 83% is excreted in the faeces and 13% in urine.

◊ References.

1. Brookman LJ, *et al.* Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; **62:** 272–8.
2. Prasad PP, *et al.* Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *J Cardiovasc Pharmacol* 2002; **40:** 801–7.

### Uses and Administration

Valsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171), to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction (p.1175), and in the management of heart failure (see under Losartan Potassium, p.1327).

Valsartan is given orally. After a dose the hypotensive effect occurs within 2 hours, reaches a peak within 4 to 6 hours, and persists for over 24 hours. The maximum hypotensive effect is achieved within 2 to 4 weeks.

In **hypertension**, valsartan is given in an initial dose of 80 mg once daily. This may be increased, if necessary, to 160 mg once daily; the maximum dose is 320 mg once daily. A lower initial dose of 40 mg once daily may be used in elderly patients over 75 years, and in those with intravascular volume depletion.

In **heart failure,** valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

In patients who have had **myocardial infarction**, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, in an initial dose of 20 mg twice daily; the dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated.

Valsartan should be used with caution in patients with hepatic or renal impairment and dose reduction may be required (see below).

◊ Reviews.

1. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54:** 299–311.
2. Ripley TL. Valsartan in chronic heart failure. *Ann Pharmacother* 2005; **39:** 460–9.
3. Mistry NB, *et al.* The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7:** 575–81.
4. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vasc Health Risk Manag* 2007; **3:** 425–30.

**Administration in children.** Valsartan may be used for hypertension in children aged 6 to 16 years. US licensed product information recommends an initial dose of 1.3 mg/kg once daily (up to a maximum of 40 mg). The dose should be adjusted according to response, but doses above 2.7 mg/kg daily have not been studied. A suspension formulation may be used (see Suspension, above) but exposure to valsartan may be higher with the suspension than with tablets. There is no experience with valsartan in children with renal impairment (creatinine clearance below 30 mL/minute per 1.73 $m^2$) and it should therefore not be used in such children.

**Administration in hepatic or renal impairment.** The elimination of valsartan may be reduced in patients with hepatic impairment or biliary obstruction and it should be used with caution, if at all, in such patients; dose reductions may be required. In the UK, valsartan is contra-indicated in patients with severe hepatic impairment, cirrhosis, or biliary obstruction. In mild to moderate hepatic impairment an initial dose of 40 mg once daily and a maximum dose of 80 mg once daily is recommended for hypertension, and the dose after myocardial infarction should not generally exceed 80 mg twice daily.

Lower doses of valsartan may also be considered in patients with renal impairment. In the UK, an initial dose of 40 mg once daily is recommended for the treatment of hypertension in patients

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.

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## 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.

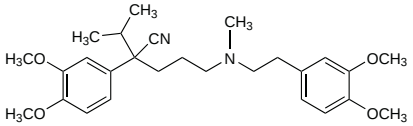
Верапамила Гидрохлорид

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

*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