the inward sodium current in cardiac cells. Flecainide, because of its sodium-channel blocking action, exaggerates this deficiency and the resulting ST-segment elevation, and aids in diagnosis; however, it may precipitate serious ventricular arrhythmias[10] and must not be used for treatment.

1. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.
2. Krapp M, *et al*. Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002; **19:** 158–64.
3. Rasheed A, *et al*. Neonatal ECG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart* 2003; **89:** 470.
4. Hall CM, Ward Platt MP. Neonatal flecainide toxicity following supraventricular tachycardia treatment. *Ann Pharmacother* 2003; **37:** 1343–4.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. CAST and beyond: implications of the cardiac arrhythmias suppression trial. *Circulation* 1990; **81:** 1123–7. [Simultaneous publication occurred in *Eur Heart J* 1990; **11:** 194–9].
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; **321:** 406–12.
7. Echt DS, *et al*. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324:** 781–8.
8. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
9. Singleton CB, McGuire MA. The Brugada syndrome: a recently recognised genetic disease causing sudden cardiac death. *Med J Aust* 2000; **173:** 415–8.
10. Gasparini M, *et al*. Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003; **26:** 338–41.

Pain. Class Ic antiarrhythmics such as flecainide are among the drugs that have been used as analgesic adjuvants in neuropathic pain (p.8), although the evidence for benefit with flecainide is limited. A positive response has been reported[1,2] in patients with severe pain due to nerve infiltration, but a controlled trial had to be stopped[3] when supplies of the drug were withdrawn after the finding of increased mortality in a study in post-infarction patients (CAST; see Cardiac Arrhythmias, above), and a later study[4] found that flecainide was effective in only a minority of patients with cancer pain. A small study[5] has suggested that flecainide may be effective in postherpetic neuralgia.

1. Dunlop R, *et al*. Analgesic effects of oral flecainide. *Lancet* 1988; **i:** 420–1.
2. Sinnott C, *et al*. Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
3. Dunlop RJ, *et al*. Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
4. Chong SF, *et al*. Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997; **13:** 112–17.
5. Ichimata M, *et al*. Analgesic effects of flecainide on postherpetic neuralgia. *Int J Clin Pharmacol Res* 2001; **21:** 15–19.

Preparations

BP 2008: Flecainide Injection; Flecainide Tablets;
USP 31: Flecainide Acetate Tablets.

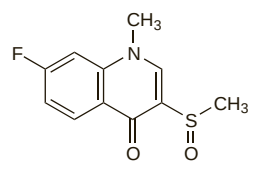
Proprietary Preparations (details are given in Part 3)
Arg.: Diondel; Tambocor†; ***Austral.:*** Flecatab; Tambocor; ***Austria:*** Aristocor; ***Belg.:*** Apocard; Tambocor; ***Canad.:*** Tambocor; ***Chile:*** Tambocor; ***Cz.:*** Tambocor; ***Denm.:*** Tambocor; ***Fin.:*** Tambocor; ***Fr.:*** Flecaine; ***Ger.:*** flecadura; Tambocor; ***Gr.:*** Tambocor; ***Hong Kong:*** Tambocor; ***Irl.:*** Tambocor; ***Israel:*** Tambocor; ***Ital.:*** Almarytm; ***Malaysia:*** Tambocor; ***Mex.:*** Tambocor; ***Neth.:*** Tambocor; ***Norw.:*** Tambocor; ***NZ:*** Tambocor; ***Philipp.:*** Tambocor; ***Port.:*** Apocard; ***S.Afr.:*** Tambocor; ***Singapore:*** Tambocor; ***Spain:*** Apocard; ***Swed.:*** Tambocor; ***Switz.:*** Tambocor; ***Thai.:*** Tambocor; ***UK:*** Tambocor; ***USA:*** Tambocor.

Flosequinan *(BAN, USAN, rINN)*

BTS-49465; Floséquinan; Flosequinán; Flosequinanum. 7-Fluoro-1-methyl-3-methylsulphinyl-4-quinolone.

Флозехинан

$C_{11}H_{10}FNO_2S$ = 239.3.
CAS — 76568-02-0.
ATC — C01DB01.
ATC Vet — QC01DB01.



Profile

Flosequinan is a direct-acting arteriovenous vasodilator that was used as an adjunct to the conventional treatment of heart failure, but was withdrawn from the market after findings of excess mortality.

◊ References.

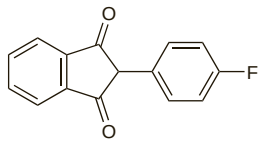
1. Kamali F, Edwards C. Possible role of metabolite in flosequinan-related mortality. *Clin Pharmacokinet* 1995; **29:** 396–403.

Fluindione *(rINN)*

Fluindiona; Fluindionum; Fluorindione; LM-123. 2-(4-Fluorophenyl)indan-1,3-dione.

Флуиндион

$C_{15}H_9FO_2$ = 240.2.
CAS — 957-56-2.



Profile

Fluindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1425). It is used in the management of thromboembolic disorders (p.1187) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p.1369), its use is limited.

The usual initial dose is 20 mg daily; the dose is then adjusted according to coagulation tests.

Preparations

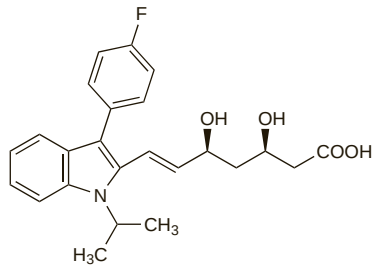
Proprietary Preparations (details are given in Part 3)
Fr.: Previscan.

Fluvastatin Sodium *(BANM, USAN, rINNM)*

Fluvastatina sódica; Fluvastatine sodique; Fluvastatinum natricum; Natrii Fluvastatinum; XU-62-320. Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate.

Натрий Флувастатин

$C_{24}H_{25}FNNaO_4$ = 433.4.
CAS — 93957-54-1 (fluvastatin); 93957-55-2 (fluvastatin sodium).
ATC — C10AA04.
ATC Vet — QC10AA04.



(fluvastatin)

Pharmacopoeias. In *US.*
USP 31 (Fluvastatin Sodium). A white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in water, in alcohol, and in methyl alcohol. A 1% solution in water has a pH of 8.0 to 10.0. Store in airtight containers at a temperature not exceeding 40°. Protect from light and moisture.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Interactions

The interactions of statins with other drugs are described under simvastatin (p.1392). Fluvastatin is metabolised mainly by the cytochrome P450 isoenzyme CYP2C9 and does not have the same interactions with CYP3A4 inhibitors as simvastatin, although caution has been advised when such combinations are used. However, interactions may occur with inhibitors of CYP2C9, such as fluconazole; use with rifampicin, a CYP2C9 inducer, may reduce the bioavailability of fluvastatin by about 50%.

Pharmacokinetics

Fluvastatin is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. Metabolism is mainly by the cytochrome P450 isoenzyme CYP2C9, with only a small amount metabolised by CYP3A4. An absolute bioavailability of about 24% has been reported. It is more than 98% bound to plasma proteins. About 90% is excreted in the faeces, mainly as metabolites, with only about 6% being excreted in the urine.

◊ General reviews.

1. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet* 2001; **40:** 263–81.

Uses and Administration

Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol, in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias). It is also given as secondary prophylaxis for cardiovascular risk reduction (p.1164) in patients with ischaemic heart disease, including patients who have had a percutaneous coronary intervention.

Fluvastatin is given orally as the sodium salt, but doses are expressed in terms of the base; 21.06 mg of fluvastatin sodium is equivalent to about 20 mg of base. The usual initial dose is 20 to 40 mg of fluvastatin once daily in the evening. This may be increased, if necessary, at intervals of 4 weeks or more, up to 80 mg daily, in two divided doses or as a once-daily modified-release preparation; patients requiring a large reduction in LDL-cholesterol may be started on the 80 mg daily dose. A dose of 80 mg daily may also be used in patients who have had a percutaneous coronary intervention.

For the use of fluvastatin in children, see below.

◊ References.

1. Langtry HD, Markham A. Fluvastatin: a review of its use in lipid disorders. *Drugs* 1999; **57:** 583–606.
2. Corsini A, *et al*. Fluvastatin: clinical and safety profile. *Drugs* 2004; **64:** 1305–23.
3. Winkler K, *et al*. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007; **29:** 1987–2000.
4. McDonald KJ, Jardine AG. The use of fluvastatin in cardiovascular risk management. *Expert Opin Pharmacother* 2008; **9:** 1407–14.

Administration in children. Fluvastatin may be used in the management of children aged 10 to 16 years with heterozygous familial hypercholesterolaemia.[1] US licensed product information recommends an initial oral dose of 20 mg once daily, increased as required, at intervals of 6 weeks, to a maximum dose of 80 mg daily in 2 divided doses or as a once-daily modified-release preparation.

1. van der Graaf A, *et al*. Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr* 2006; **95:** 1461–6.

Preparations

USP 31: Fluvastatin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Lescol; ***Austral.:*** Lescol; Vastin; ***Austria:*** Lescol; ***Belg.:*** Lescol; ***Braz.:*** Lescol; ***Canad.:*** Lescol; ***Cz.:*** Lescol; ***Denm.:*** Canef; Lescol; ***Fin.:*** Canef; Lescol; ***Fr.:*** Fractal; Lescol; ***Ger.:*** Cranoc; LOCOL; ***Gr.:*** Hovalin; Lescol; ***Hong Kong:*** Lescol; ***Hung.:*** Lescol; Lochol; ***Indon.:*** Lescol; ***Irl.:*** Lescol; ***Israel:*** Lescol; ***Ital.:*** Lescol; Lipaxan; Primesin; ***Jpn:*** Lochol; ***Malaysia:*** Lescol; ***Mex.:*** Canef†; Lescol; ***Neth.:*** Canef; Lescol; Vaditon; ***Norw.:*** Lescol; ***NZ:*** Lescol†; ***Philipp.:*** Lescol; ***Pol.:*** Lescol; ***Port.:*** Canef; Cardiol; Lescol; ***Rus.:*** Lescol (Лескол); ***S.Afr.:*** Lescol; ***Singapore:*** Lescol; ***Spain:*** Digaril; Lescol; Liposit; Lymetel; Princess Prolib†; Vaditon; ***Swed.:*** Canef; Lescol; ***Switz.:*** Lescol; Primesin; ***Thai.:*** Lescol; ***Turk.:*** Lescol; ***UK:*** Lescol; ***USA:*** Lescol; ***Venez.:*** Lescol†.

Fondaparinux Sodium *(BAN, USAN, rINN)*

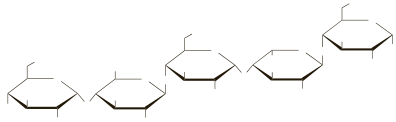
Fondaparin Sodium; Fondaparinuks Sodyum; Fondaparinuuksinatrium; Fondaparinux sódico; Fondaparinux Sodique; Fondaparinuxnatrium; Fondaparinuxum Natricum; Fondaparinuxum Natrium; Org-31540; SR-90107A.

Фондапаринукс Натрия

CAS — 114870-03-0.

ATC — B01AX05.

ATC Vet — QB01AX05.



(fondaparinux)

Adverse Effects

As for Heparin, p.1301.

Treatment of Adverse Effects

If bleeding occurs fondaparinux should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for fondaparinux (but see below).

Overdosage. Activated eptacog alfa (recombinant factor VIIa) given 2 hours after an injection of fondaparinux was found[1] in healthy subjects to normalise coagulation times and thrombin generation for up to 6 hours, suggesting that it may be useful to treat bleeding complications, or if acute surgery is needed.

1. Bijsterveld NR, *et al.* Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; **106:** 2550–54.

Precautions

As for Heparin, p.1303.

Fondaparinux should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) in the presence of fondaparinux itself.

Fondaparinux is contra-indicated in severe renal impairment, and special care is required in patients with body-weight below 50 kg.

Interactions

As for Heparin, p.1303.

Pharmacokinetics

After subcutaneous injection fondaparinux sodium is rapidly and completely absorbed, with bioavailability of 100%. It is extensively bound in plasma, predominantly to antithrombin III. It is excreted in the urine, with 64 to 77% of a dose excreted unchanged. The elimination half-life is between 17 and 21 hours, but is prolonged in patients with renal impairment, in the elderly, and in those weighing less than 50 kg.

◊ References.

1. Donat F, *et al.* The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; **41** (suppl 2): 1–9.
2. Paolucci F, *et al.* Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin Pharmacokinet* 2002; **41** (suppl 2): 11–18.

Pregnancy. Although an *in vitro* study[1] reported that fondaparinux does not cross the placenta, a small study[2] in pregnant women who had received fondaparinux found that anti-factor Xa activity was elevated in umbilical cord blood, suggesting that a small amount of placental transfer had taken place.

1. Lagrange F, *et al.* Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet* 2002; **41** (suppl 2): 47–9.
2. Dempfle C-EH. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; **350:** 1914–15.

Uses and Administration

Fondaparinux is a synthetic pentasaccharide that acts as a selective inhibitor of activated factor X. It is used as the sodium salt as an anticoagulant in the management of venous thromboembolism (p.1189), unstable angina (p.1157), and acute myocardial infarction (p.1175). It has also been used in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Adverse Effects of Heparin, p.1302).

For *prophylaxis* of **venous thromboembolism** in abdominal and orthopaedic surgery, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily, starting 6 to 8 hours after surgery and continued for at least 5 to 9 days, or up to 32 days in hip fracture. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6 to 14 days.

In the initial *treatment* of venous thromboembolism, fondaparinux sodium is given by subcutaneous injection once daily at a dose of 5 mg for patients weighing less than 50 kg, 7.5 mg for weight 50 to 100 kg, and 10 mg for weight over 100 kg. Treatment is usually continued for 5 to 9 days, and at least until oral anticoagulation is established.

Fondaparinux is also used in **unstable angina** and acute ST-elevation **myocardial infarction**, but is only indicated in patients for whom urgent percutaneous coronary intervention is not planned. It is given in a dose of 2.5 mg subcutaneously once daily for up to 8 days, with the first dose given intravenously in acute ST-elevation myocardial infarction. Heparin should be given at the time of the procedure if percutaneous coronary intervention is performed and fondaparinux should be restarted when clinically appropriate.

Doses of fondaparinux may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Keam SJ, Goa KL. Fondaparinux sodium. *Drugs* 2002; **62:** 1673–85.
2. Tran AH, Lee G. Fondaparinux for prevention of venous thromboembolism in major orthopedic surgery. *Ann Pharmacother* 2003; **37:** 1632–43.
3. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; **349:** 1695–1702.
4. Reynolds NA, *et al.* Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. *Drugs* 2004; **64:** 1575–96.
5. Büller HR, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; **140:** 867–73.
6. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295:** 1519–30.
7. Cohen AT, *et al.* ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Abridged version: *BMJ* 2006; **332:** 325–9. Full version: http://www.bmj.com/cgi/reprint/332/7537/325 (accessed 14/05/08)
8. Yusuf S, *et al.* Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.
9. Efird LE, Kockler DR. Fondaparinux for thromboembolic treatment and prophylaxis of heparin-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 1383–7.

Administration in renal impairment. Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. US licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 30 mL/minute, and advises caution in those with CC between 30 and 50 mL/minute. UK licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 20 mL/minute; for patients with CC between 20 and 50 mL/minute a subcutaneous dose of 1.5 mg once daily is recommended for prophylaxis of venous thromboembolism, but no dosage alteration is required for unstable angina or myocardial infarction.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Arixtra; ***Belg.:*** Arixtra; ***Braz.:*** Arixtra; ***Canad.:*** Arixtra; ***Cz.:*** Arixtra; ***Denm.:*** Arixtra; ***Fin.:*** Arixtra; ***Fr.:*** Arixtra; ***Ger.:*** Arixtra; ***Gr.:*** Arixtra; ***Hong Kong:*** Arixtra†; ***Indon.:*** Arixtra; ***Ital.:*** Arixtra; ***Malaysia:*** Arixtra; ***Mex.:*** Arixtra; ***Neth.:*** Arixtra; Quixidar; ***Norw.:*** Arixtra; ***NZ:*** Arixtra†; ***Pol.:*** Arixtra; ***Port.:*** Arixtra; Quixidar†; ***Rus.:*** Arixtra (Арикстра); ***Singapore:*** Arixtra; ***Spain:*** Arixtra; ***Swed.:*** Arixtra; ***Switz.:*** Arixtra; ***Thai.:*** Arixtra; ***UK:*** Arixtra; ***USA:*** Arixtra.

Fosinopril Sodium *(BANM, USAN, rINNM)*

Fosinopriilinatrium; Fosinopril sódico; Fosinopril sodique; Fosinopril Sodyum; Fosinoprilnatrium; Fosinoprilum natricum; Natrii Fosinoprilum; SQ-28555. (4*S*)-4-Cyclohexyl-1-{[(*RS*)-2-methyl-1-(propionyloxy)propoxy]-(4-phenylbutyl)phosphinylacetyl}-L-proline sodium.

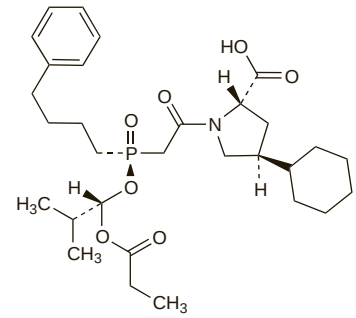
Натрий Фозиноприл

$C_{30}H_{45}NNaO_7P$ = 585.6.

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.



(fosinopril)

Pharmacopoeias. In *US*.

USP 31 (Fosinopril Sodium). Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat are achieved about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

◊ References.

1. Singhvi SM, *et al.* Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; **25:** 9–15.
2. Kostis JB, *et al.* Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; **58:** 660–5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with varying degrees of impairment,[1-5] including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al.* Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; **49:** 457–67.
2. Gehr TWB, *et al.* Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; **41:** 165–9.
3. Sica DA, *et al.* Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; **20:** 420–7.
4. Gehr TWB, *et al.* The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; **45:** 431–6.
5. Greenbaum R, *et al.* Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; **49:** 23–31.