These are given in Table 6, below. An INR within 0.5 units of the target value in the UK is generally considered satisfactory. In the USA it is recommended that the INR be maintained at the mid-level of the range. An INR less than 2.0 generally represents inadequate anticoagulation and an INR above 4.5 represents greater risk of haemorrhage.

Measurements should be carried out before treatment and then daily or on alternate days in the early stages of treatment. Once the dose has been established and the patient well stabilised the measurement can be made at greater but regular intervals, for example every 8 weeks; allowances should be made for any events that might influence the activity of the anticoagulant. Self-monitoring may be appropriate in some patients.

◊ General references.

1. Harrington R, Ansell J. Risk-benefit assessment of anticoagulant therapy. *Drug Safety* 1991; **6:** 54–69.
2. Le DT, *et al.* The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. *Ann Intern Med* 1994; **120:** 552–8.
3. British Society for Haematology: British Committee for Standards in Haematology—Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation: third edition. *Br J Haematol* 1998; **101:** 374–87. Also available at: http://www.bcshguidelines.com/pdf/bjh715.pdf (accessed 25/02/05) Updated 2005 guidelines. Update: Baglin T, *et al*, for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition—2005 update. *Br J Haematol* 2006; **132:** 277–85. Also available at: http://www.bcshguidelines.com/pdf/oralanticoagulation.pdf (accessed 07/06/06)
4. Hardman SMC, Cowie MR. Anticoagulation in heart disease. *BMJ* 1999; **318:** 238–44.
5. Gage BF, *et al.* Management and dosing of warfarin therapy. *Am J Med* 2000; **109:** 481–8.
6. Hirsh J, *et al.* American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 2003; **107:** 1692–1711. Also available at: http://circ.ahajournals.org/cgi/reprint/107/12/1692.pdf (accessed 25/02/05)
7. Fitzmaurice DA, *et al.* British Society of Haematology Taskforce for Haemostasis and Thrombosis. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol* 2005; **131:** 156–65. Correction. *ibid.* 2006; **132:** 118. Also available at: http://www.bcshguidelines.com/pdf/fitzmaurice_100306.pdf (accessed 27/05/08)
8. Ansell J, *et al.* Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 160S–198S.

Administration and dosage. Algorithms and guidelines have been developed for beginning anticoagulant therapy, based on the method of Fennerty *et al.*[1] Although a loading dose of 10 mg daily for 2 days (depending on the INR) has been widely used, lower doses may be more appropriate, especially in hospitalised patients at greater risk of over-anticoagulation. Studies[2-4] comparing warfarin loading doses of 5 and 10 mg found that for both groups a therapeutic INR in the range of 2.0 to 3.0 was reached in most patients by day 5 of treatment. Although a study of outpatients with venous thromboembolism[5] found that a therapeutic INR was achieved 1.4 days sooner with the larger loading dose, the nomogram used was not designed for inpatients.

In situations where rapid anticoagulation is not necessary, loading doses may not be required and treatment should begin with the estimated maintenance dose. Studies[6,7] have found that the maintenance dose decreases with age and is lower in women than in men, and lower initial doses are therefore recommended in the elderly. Regimens that have been suggested include warfarin in a dose of 4 mg daily for 3 days, then adjusted according to the INR,[8] or, for patients requiring anticoagulation prophylaxis, 2 mg daily for 2 weeks followed by weekly adjustment using an algorithm until the target INR is reached.

1. Fennerty A, *et al.* Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ* 1984; **288:** 1268–70.
2. Harrison L, *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; **126:** 133–6.
3. Crowther MA, *et al.* Warfarin: less may be better. *Ann Intern Med* 1997; **127:** 333.
4. Crowther MA, *et al.* A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; **159:** 46–8.
5. Kovacs MJ, *et al.* Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003; **138:** 714–19.
6. Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. *Am J Health-Syst Pharm* 2005; **62:** 1062–6.
7. Garcia D, *et al.* Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005; **127:** 2049–56.
8. Siguret V, *et al.* Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005; **118:** 137–42.

Administration in infants and children. Increasing numbers of infants and children are receiving anticoagulants for prophylaxis and treatment of thromboembolism. Doses of warfarin and therapeutic INR ranges have been adapted from adult therapy but cohort studies[1,2] of paediatric patients have found that warfarin requirements may be affected by a number of factors including age, and the use of infant formulas supplemented with vitamin K. Recommendations[3] for the use of oral anticoagulants in children have been published.

1. Tait RC, *et al.* Oral anticoagulation in paediatric patients: dose requirements and complications. *Arch Dis Child* 1996; **74:** 228–31.
2. Streif W, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999; **94:** 3007–14.
3. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Catheters and cannulas. For mention of the use of oral anticoagulants to prevent thrombosis in patients with indwelling infusion devices, see Heparin Sodium, p.1304.

Connective tissue and muscular disorders. Warfarin has been proposed to treat subcutaneous calcium deposition (calcinosis cutis) in patients with dermatomyositis, but its value is disputed, see Polymyositis and Dermatomyositis, p.1510.

Table 6. Recommended International Normalised Ratios (INR).

	INR	Condition or procedure
UK	2.5	Pulmonary embolism; deep-vein thrombosis; recurrence of venous thromboembolism when no longer on warfarin; symptomatic inherited thrombophilia; venous thromboembolism associated with antiphospholipid syndrome; atrial fibrillation; mural thrombus; cardiomyopathy; bioprosthetic heart valves.
	2.5 or 3.0	Cardioversion (higher INR may be appropriate before procedure); some mechanical prosthetic heart valves.
	3.5	Recurrence of venous thromboembolism when on warfarin; some mechanical prosthetic heart valves.
US	2.0 to 3.0	Prophylaxis of venous thromboembolism in high-risk surgical patients; treatment of venous thrombosis and pulmonary embolism; prophylaxis of systemic embolism in patients with atrial fibrillation, valvular heart disease, bioprosthetic heart valves or some mechanical prosthetic heart valves; prevention of recurrent myocardial infarction in patients receiving aspirin.
	2.5 to 3.5	Prophylaxis in patients with some mechanical prosthetic heart valves.
	3.0 to 4.0	Prevention of recurrent myocardial infarction in patients not receiving aspirin; systemic embolism in patients with some mechanical heart valves.

Preparations

BP 2008: Warfarin Tablets;
USP 31: Warfarin Sodium for Injection; Warfarin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Circuvit; Coumadin; ***Austral.:*** Coumadin; Marevan; ***Belg.:*** Marevan; ***Braz.:*** Coumadin; Marevan; ***Canad.:*** Coumadin; ***Chile:*** Coumadin; ***Cz.:*** Lawarin; ***Denm.:*** Marevan; ***Fin.:*** Marevan; ***Fr.:*** Coumadine; ***Ger.:*** Coumadin; ***Gr.:*** Marevan; Panwarfin; ***Hung.:*** Marfarin; ***India:*** Uniwarfin; Warf; ***Indon.:*** Simarc-2; ***Irl.:*** Warfant; ***Israel:*** Coumadin; ***Ital.:*** Coumadin; ***Malaysia:*** Coumadin; Orfarin; ***Mex.:*** Coumadin; ***Norw.:*** Marevan; ***NZ:*** Coumadin; Marevan; ***Philipp.:*** Coumadin; ***Port.:*** Varfine; ***Rus.:*** Warfarex (Варфарекс); ***S.Afr.:*** Coumadin†; ***Singapore:*** Coumadin; Marevan; Orfarin; ***Spain:*** Aldocumar; Tedicumar; ***Swed.:*** Waran; ***Thai.:*** Befarin; Fargem; Maforan; Orfarin; ***Turk.:*** Coumadin; Orfarin; ***UK:*** Marevan; ***USA:*** Coumadin; Jantoven; ***Venez.:*** Anasmol; Coumadin; Cumar.

Xamoterol Fumarate *(BANM, USAN, rINNM)*

Fumarato de xamoterol; ICI-118587; Ksamoterolfumarat; Ksamoterolifumaraatti; Xamotérol, Fumarate de; Xamoteroli Fumaras. *N*-{2-[2-Hydroxy-3-(4-hydroxyphenoxy)propylamino]-ethyl}morpholine-4-carboxamide fumarate.

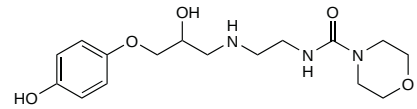
Ксамотерола Фумарат

$(C_{16}H_{25}N_3O_5)_2,C_4H_4O_4$ = 794.8.

CAS — 81801-12-9 (xamoterol); 90730-93-1 (xamoterol fumarate).

ATC — C01CX07.

ATC Vet — QC01CX07.



(xamoterol)

Profile

Xamoterol is a beta-adrenoceptor partial agonist with a selective action on beta$_1$ receptors. As a partial agonist it exerts mainly agonist activity at rest and under conditions of low sympathetic drive which results in improved ventricular function and increased cardiac output; during exercise and during conditions of increased sympathetic drive, such as that occurring in severe heart failure, xamoterol exerts beta-blocking activity. It therefore has the properties of both sympathomimetics (see p.1407) and beta blockers (see p.1225).

Xamoterol has been used in the management of chronic mild heart failure but was associated with deterioration and an excess of deaths in those with more severe disease. It has also been used in orthostatic hypotension secondary to autonomic failure.

◊ References.

1. Anonymous. Xamoterol—more trouble than it's worth? *Drug Ther Bull* 1990; **28:** 53–4.
2. Anonymous. New evidence on xamoterol. *Lancet* 1990; **336:** 24.
3. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990; **336:** 1–6.

Xantinol Nicotinate *(BAN, rINN)*

Ksantinolinikotinaatti; Ksantynolu nikotynian; Nicotinato de xantinol; SK-331A; Xanthinol Niacinate *(USAN)*; Xanthinol Nicotinate; Xanthinol nikotinát; Xantinol, Nicotinate de; Xantinoli Nicotinas; Xantinolnikotinat. 7-{2-Hydroxy-3-[(2-hydroxyethyl)methylamino]propyl}theophylline nicotinate.

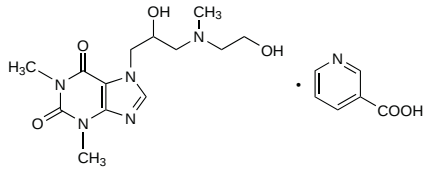
Ксантинола Никотинат

$C_{13}H_{21}N_5O_4,C_6H_5NO_2$ = 434.4.

CAS — 437-74-1.

ATC — C04AD02.

ATC Vet — QC04AD02.



Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Xantinol nicotinate is a vasodilator with general properties similar to those of nicotinic acid (p.1957), to which it is slowly hydrolysed. Xantinol nicotinate is used in the management of peripheral (p.1178) and cerebral vascular disorders (p.1165) and in hyperlipidaemias (p.1169). Oral doses of up to 3 g daily may be given. It has also been given by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Frigol; ***Cz.:*** Xanidil; ***Ger.:*** Complamin spezial; ***Hung.:*** Xavin; ***India:*** Complamina; ***Ital.:*** Complamin; Vedrin†; ***Neth.:*** Complamin; ***Pol.:*** Sadamin; ***Switz.:*** Complamin.

Multi-ingredient: ***Spain:*** Rulun.

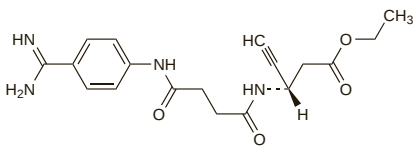
Xemilofiban Hydrochloride *(USAN, rINNM)*

Hidrocloruro de xemilofibán; SC-54684A; Xémilofiban, Chlorhydrate de; Xemilofibani Hydrochloridum. Ethyl (3*S*)-3-{3-[(*p*-amidinophenyl)carbamoyl]propionamido}-4-pentynoate monohydrochloride.

Ксемилофибана Гидрохлорид

$C_{18}H_{22}N_4O_4,HCl$ = 394.9.

CAS — 149820-74-6 (xemilofiban); 156586-91-3 (xemilofiban hydrochloride).



(xemilofiban)

Profile

Xemilofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug for the management of thromboembolic disorders such as unstable angina, and after angioplasty, but results have been disappointing.

◊ References.

1. O'Neill WW, *et al.* Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. *N Engl J Med* 2000; **342:** 1316–24.

Xipamide *(BAN, USAN, rINN)* ⊗

Be-1293; Ksipamidi; MJF-10938; Xipamid; Xipamida; Xipamidum. 4-Chloro-5-sulphamoylsalicylo-2′,6′-xylidide; 5-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxy-benzamide.

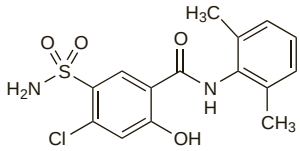
Ксипамид

$C_{15}H_{15}ClN_2O_4S$ = 354.8.

CAS — 14293-44-8.

ATC — C03BA10.

ATC Vet — QC03BA10.



Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Effects on electrolyte balance. Although reductions in plasma-potassium concentrations with xipamide have been shown to be on average comparable with those produced by thiazide and loop diuretics at equipotent doses,[1] there have been several reports of marked hypokalaemia in individual patients. Asymptomatic hypokalaemia was reported in 4 of 5 patients[2] (serum-potassium concentrations of less than 3.4 mmol/litre) and in 3 of 13 patients[3] (serum-potassium concentrations of less than 3.0 mmol/litre). Severe hypokalaemia resulting in ventricular arrhythmias has been reported after xipamide used alone[4] or with indapamide.[5] Profound electrolyte disturbances with altered consciousness and ventricular extrasystoles occurred in a patient taking digoxin after the addition of xipamide for 10 days.[6] A case of hypokalaemic periodic paralysis associated with xipamide use has also been reported.[7]

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.
2. Weissberg P, Kendall MJ. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
3. Raftery EB, *et al.* A study of the antihypertensive action of xipamide using ambulatory intra-arterial monitoring. *Br J Clin Pharmacol* 1981; **12:** 381–5.
4. Altmann P, Hamblin JJ. Ventricular fibrillation induced by xipamide. *BMJ* 1982; **284:** 494.
5. Boulton AJM, Hardisty CA. Ventricular arrhythmias precipitated by treatment with non-thiazide diuretics. *Practitioner* 1982; **226:** 125–8.
6. Bentley J. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
7. Boulton AJM, Hardisty CA. Hypokalaemic periodic paralysis precipitated by diuretic therapy and minor surgery. *Postgrad Med J* 1982; **58:** 106–7.

Hepatic impairment. For a recommendation that xipamide should be given with caution to patients with liver disease, see under Pharmacokinetics, below.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Xipamide has been reported to be well absorbed from the gastrointestinal tract. Absorption is fairly rapid with peak plasma concentrations occurring within 1 or 2 hours of oral doses. It is 99% bound to plasma proteins, and is excreted in the urine, partly unchanged and partly in the form of the glucuronide metabolite. It is reported to have a plasma half-life of about 5 to 8 hours. In patients with renal impairment excretion in the bile becomes more prominent.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Hepatic impairment. Xipamide was present in the plasma and in ascitic fluid in patients with liver cirrhosis in proportion to the protein content of the respective compartments.[1] The amount of drug excreted into the urine was much greater in patients with liver disease than in healthy control subjects. This was attributed to a diminution in hepatic elimination, which could result in significant effects on the clinical response to xipamide. Thus patients with cholestasis could have an enhanced response to xipamide. On the other hand cirrhotic patients with the hepatorenal syndrome may be resistant to diuretics. Xipamide should be used with caution in patients with liver disease.

1. Knauf H, *et al.* Xipamide disposition in liver cirrhosis. *Clin Pharmacol Ther* 1990; **48:** 628–32.

Renal impairment. After single oral and intravenous doses of xipamide 20 mg the drug appeared to be completely absorbed from the gastrointestinal tract.[1] The mean elimination half-life in healthy subjects was 7 hours and two-thirds of the clearance was by extrarenal routes. There was some accumulation in patients with chronic renal failure, with a calculated elimination half-life of 9 hours in end-stage renal disease.

1. Knauf H, Mutschler E. Pharmacodynamics and pharmacokinetics of xipamide in patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; **26:** 513–20.

Uses and Administration

Xipamide is a diuretic, structurally related to indapamide, with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis begins about 1 or 2 hours after an oral dose, reaches a peak at 4 to 6 hours, and lasts for about 12 hours.

In the treatment of **hypertension** the usual dose is 20 mg daily as a single morning dose, either alone, or with other antihypertensives. In some patients a dose of 10 mg daily may be adequate. In the treatment of **oedema** the usual initial dose is 40 mg daily, subsequently reduced to 20 mg daily, according to response; in resistant cases 80 mg daily may be required.

◊ References.

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Aquaphoril; ***Fr.:*** Lumitens†; ***Ger.:*** Aquaphor; Aquex; Xipa; Xipalsis; Xipagamma; ***India:*** Xipamid; ***Ital.:*** Aquafor†; ***Port.:*** Diurexan; ***S.Afr.:*** Diurexan†; ***Spain:*** Demiax†; Diurex; ***UK:*** Diurexan.

Multi-ingredient: ***Ger.:*** Durotan†; Neotri.

Zofenopril Calcium *(BANM, USAN, rINNM)*

Calcii Zofenoprilum; SQ-26991; Zofenopril cálcico; Zofénopril Calcique. Calcium salt of (4*S*)-1-[(2*S*)-3-(Benzylthio)-2-methylpropionyl]-4-(phenylthio)-L-proline.

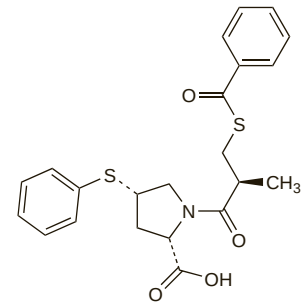
Кальций Зофеноприл

$C_{44}H_{44}CaN_2O_8S_4$ = 897.2.

CAS — 81872-10-8 (zofenopril); 81938-43-4 (zofenopril calcium).

ATC — C09AA15.

ATC Vet — QC09AA15.



(zofenopril)

Profile

Zofenopril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171) and myocardial infarction (p.1175). It owes its activity to the active metabolite zofenoprilat (SQ-26333) to which it is converted after oral doses. It is given orally in a usual daily maintenance dose of 30 to 60 mg of the calcium salt, as a single dose or in two divided doses.

◊ References.

1. Ambrosioni E, *et al.* The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995; **332:** 80–5.
2. Borghi C, *et al.* Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension: SMILE study investigators: Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens* 1999; **12:** 665–72.
3. Borghi C, *et al.* A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. *Expert Opin Pharmacother* 2004; **5:** 1965–77.
4. Buikema H. Use of the ACE inhibitor zofenopril in the treatment of ischemic heart disease. *Expert Rev Cardiovasc Ther* 2006; **4:** 631–47.
5. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. *Am J Cardiovasc Drugs* 2007; **7:** 17–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Bifril; ***Fr.:*** Zofenil; ***Gr.:*** Zofepril; Zopranol; ***Irl.:*** Zofenil; ***Ital.:*** Bifril; Zantipres; Zopranol; ***Neth.:*** Zofil; Zopranol; ***Port.:*** Zofenil; Zopranol; ***Rus.:*** Zocardis (Зокардис); ***Spain:*** Zofenil; Zopranol; ***Swed.:*** Bifril†; ***Switz.:*** Zofenil; ***Turk.:*** Zoprotec.

Multi-ingredient: ***Fr.:*** Zofenilduo; ***Gr.:*** Zofepril Plus; Zopranol Plus; ***Ital.:*** Bifrizide; Zantipride; Zoprazide; ***Port.:*** Zofenil Plus.