Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dopacard†; ***Denm.:*** Dopacard; ***Fin.:*** Dopacard; ***Fr.:*** Dopacard; ***Ger.:*** Dopacard; ***Irl.:*** Dopacard; ***NZ:*** Dopacard†; ***Swed.:*** Dopacard†; ***Switz.:*** Dopacard†; ***UK:*** Dopacard.

Doxazosin Mesilate *(BANM, rINNM)*

Doksazosyny mezylan; Doxazosin Mesylate *(USAN)*; Doxazosin Methanesulphonate; Doxazosine, mésilate de; Doxazosini mesilas; Doxazosin-mesylát; Mesilato de doxazosina; UK-33274-27. 1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulphonate.

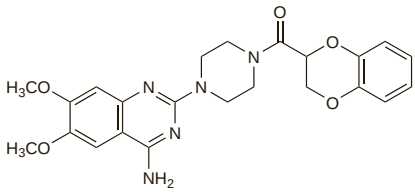
Доксазозина Мезилат

$C_{23}H_{25}N_5O_5,CH_3SO_3H$ = 547.6.

CAS — 74191-85-8 (doxazosin); 77883-43-3 (doxazosin mesilate).

ATC — C02CA04.

ATC Vet — QC02CA04.



(doxazosin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*.
Ph. Eur. 6.2 (Doxazosin Mesilate). A white or almost white crystalline powder. It exhibits polymorphism and some forms may be hygroscopic. Slightly soluble in water and in methyl alcohol; soluble in a mixture of 15 volumes of water and 35 volumes of tetrahydrofuran; practically insoluble in acetone. Store in airtight containers.
USP 31 (Doxazosin Mesylate). A white to tan-coloured powder. Very slightly soluble in water and in methyl alcohol; freely soluble in formic acid. Store at a temperature below 30°.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375.

Effects on mental function. For a report of acute psychosis associated with doxazosin use, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Hypotension. Six of 18 hypertensive patients had first-dose orthostatic hypotension after receiving doxazosin 1 mg; three others had substantial but asymptomatic reductions in supine systolic blood pressure after the first dose.[1] The effect might have been exacerbated since all these patients were also receiving beta blockers or diuretics, or both. A further patient, who was also taking methyldopa, withdrew from the study with persistent orthostatic hypotension.

1. Oliver RM, *et al.* The pharmacokinetics of doxazosin in patients with hypertension and renal impairment. *Br J Clin Pharmacol* 1990; **29:** 417–22.

Urinary incontinence. For reference to urinary incontinence associated with doxazosin, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Pharmacokinetics

Doxazosin is well absorbed after oral doses, peak plasma concentrations occurring 2 to 3 hours after a dose. Oral bioavailability is about 65%. It is extensively metabolised in the liver, and excreted in faeces as metabolites and a small amount of unchanged drug. Elimination from plasma is biphasic, with a mean terminal half-life of about 22 hours. The pharmacokinetics are not altered in patients with renal impairment. Doxazosin is about 98% bound to plasma proteins and is not removed by dialysis.

◊ Reviews.

1. Elliott HL, *et al.* Pharmacokinetic overview of doxazosin. *Am J Cardiol* 1987; **59:** 78G–81G.

Uses and Administration

Doxazosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions and uses similar to those of prazosin (p.1376), but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction (below).

Doxazosin is given orally as the mesilate, but doses are usually expressed in terms of the base. Doxazosin mesilate 1.2 mg is equivalent to about 1 mg of doxazosin. After an oral dose maximum reduction in blood pressure is reported to occur in 2 to 6 hours and the effects are maintained for 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose, the initial dose is 1 mg, preferably at bedtime. Dosage may be increased after 1 or 2 weeks according to response. Usual maintenance doses for **hypertension** are up to 4 mg once daily; doses of 16 mg daily should not be exceeded. For **benign prostatic hyperplasia** the usual maintenance dose is 2 to 4 mg daily; doses of 8 mg daily should not be exceeded.

Doxazosin may also be given as a modified-release preparation.

◊ Reviews.

1. Fulton B, *et al.* Doxazosin: an update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. *Drugs* 1995; **49:** 295–320.

Benign prostatic hyperplasia. References to the use of doxazosin in patients with benign prostatic hyperplasia (p.2178).

1. Doggrell SA. After ALLHAT: doxazosin for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2004; **5:** 1957–64.
2. MacDonald R, *et al.* Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int* 2004; **94:** 1263–70.
3. Goldsmith DR, Plosker GL. Doxazosin gastrointestinal therapeutic system: a review of its use in benign prostatic hyperplasia. *Drugs* 2005; **65:** 2037–47.
4. Wilt TJ, MacDonald R. Doxazosin in the treatment of benign prostatic hypertrophy: an update. *Clin Interv Aging* 2006; **1:** 389–401.
5. Bhardwa J, *et al.* Finasteride and doxazosin alone or in combination for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2007; **8:** 1337–44.

Hypertension. Alpha blockers are among the drug groups that have been used as first-line therapy for hypertension (p.1171). However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] the doxazosin arm of the study was terminated early due to an increased incidence of heart failure in patients receiving doxazosin compared with those receiving chlortalidone and alpha blockers are now only recommended for third-line therapy unless indicated for another reason.

1. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; **283:** 1967–75. Correction. *ibid.* 2002; **288**: 2976.

Pain. For reference to the use of doxazosin in pain, see under Uses of Phentolamine Mesilate, p.1371.

Preparations

USP 31: Doxazosin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardura; Doxasin; Doxolbran; Lafedoxin; Prostazosina; Vazosin; ***Austria:*** Adoxa; Ascalan; Doxano†; Doxapress; Hibadren; Prostadilat; Supressin; ***Braz.:*** Carduran; Doxsol; Euprostatin; Prodil†; Unoprost; Zoflux; ***Canad.:*** Cardura; ***Chile:*** Alfadoxin; Angicon; Cardura; Dorbantil; ***Cz.:*** Cardura; Dosano; Dozone; Kamiren; Windoxa; Zoxon; ***Denm.:*** Biozosin; Cardosin; Carduran; Doxacar†; ***Fr.:*** Zoxan; ***Ger.:*** Alfamedin; Cardular; Diblocin; Doxa-Puren; Doxacor; Doxagamma; Doxamax†; DoxaUro†; Doxazoflo; Doxazomerck†; Jutalar; Uriduct; ***Gr.:*** Cardura; Maguran; Protectura; ***Hong Kong:*** Cardura; Doxasyn; ***Hung.:*** Cardura; Doxagal; Doxicard; ***India:*** Doxacard; ***Indon.:*** Cardura; ***Irl.:*** Cardura; Doxatan; ***Israel:*** Cadex; Cardoral; Doxaloc; ***Ital.:*** Benur; Cardura; Dedralen; Normothen; ***Jpn:*** Cardenalin†; ***Malaysia:*** Cardura; Magurol; Pencor; ***Mex.:*** Cardura; ***Neth.:*** Cardura; Progandol; Zoxan; ***Norw.:*** Carduran; ***NZ:*** Cardoxan; Dosan; ***Pol.:*** Apo-Doxan; Cardura; Doxanorm; Doxar; Doxaratio; Doxonex; Kamiren; Prostatic; Vaxosin; Zoxon; ***Port.:*** Cardura; ***Rus.:*** Artezine (Артезин); Cardura (Кардура); Kamiren (Камирен); Magurol (Магурол); Tonocardin (Тонокардин); Zoxon (Зоксон); ***S.Afr.:*** Cardugen; Cardura; ***Singapore:*** Cardura; Pencor; ***Spain:*** Carduran; Doxatensa; Doximax Neo; Progandol; ***Swed.:*** Alfadil; ***Switz.:*** Cardura; ***Thai.:*** Cardura; Carxasin; Cazosin; Dezcard; Dozozin; Duracard; Genzosin; Pencor; ***Turk.:*** Cardura; Doksura; Doxacor; ***UK:*** Cardura; Doxadura; ***USA:*** Cardura; ***Venez.:*** Cardura.

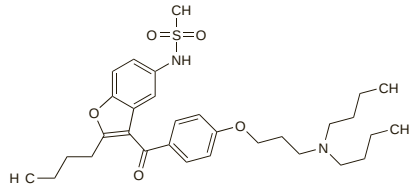
Dronedarone *(rINN)*

Dronedarona; Dronédarone; Dronedaronum; SR-33589. *N*-(2-Butyl-3-{*p*-[3-(dibutylamino)propoxy]benzoyl}-5-benzofuranyl)methanesulfonamide.

Дронедарон

$C_{31}H_{44}N_2O_5S$ = 556.8.

CAS — 141626-36-0.



Profile

Dronedarone is structurally related to amiodarone and is under investigation as an antiarrhythmic.

◊ References.

1. Touboul P, *et al.* Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003; **24:** 1481–7.
2. Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007; **41:** 599–605.
3. Singh BN, *et al.* EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; **357:** 987–99.

Duteplase *(rINN)*

Duteplasa; Dutéplase; Duteplasum; 245-L-Methionine Plasminogen Activator; SM-9527.

Дутеплаза

$C_{2736}H_{4174}N_{914}O_{824}S_{46}$ = 64529.0.

CAS — 120608-46-0.

Profile

Duteplase is a thrombolytic drug. It is a biosynthetic derivative of endogenous tissue plasminogen activator and has been used similarly to alteplase (p.1207) in the treatment of thromboembolic disorders, particularly acute myocardial infarction.

◊ References.

1. Hayashi H, *et al.* Effects of intravenous SM-9527 (double-chain tissue plasminogen activator) on left ventricular function in the chronic stage of acute myocardial infarction. *Clin Cardiol* 1993; **16:** 409–14.
2. Malcolm AD, *et al.* ESPRIT: a European study of the prevention of reocclusion after initial thrombolysis with duteplase in acute myocardial infarction. *Eur Heart J* 1996; **17:** 1522–31.

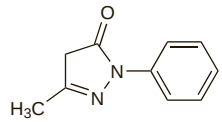
Edaravone *(rINN)*

Edaravona; Édaravone; Edaravonum; MCI-186; Norphenazone. 3-Methyl-1-phenyl-2-pyrazolin-5-one.

Эдаравон

$C_{10}H_{10}N_2O$ = 174.2.

CAS — 89-25-8.



Profile

Edaravone is a free-radical scavenger used in the management of acute ischaemic stroke (p.1185). It is given by intravenous infusion in a dose of 30 mg twice daily, infused over 30 minutes, beginning within 24 hours of stroke onset and continued for up to 14 days.

◊ References.

1. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003; **15:** 222–9.
2. Tsujita K, *et al.* Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 481–4.
3. Tsujita K, *et al.* Long-term efficacy of edaravone in patients with acute myocardial infarction. *Circ J* 2006; **70:** 832–7.
4. Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; **11:** 292–6.
5. Watanabe T, *et al.* The novel antioxidant edaravone: from bench to bedside. *Cardiovasc Ther* 2008; **26:** 101–14.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Radicut.

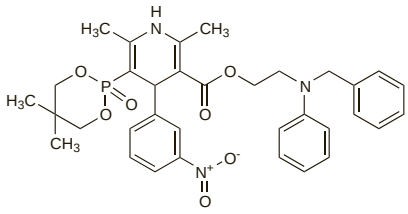
Efonidipine Hydrochloride *(rINNM)*

Éfonidipine, Chlorhydrate d'; Efonidipini Hydrochloridum; Hidrocloruro de efonidipino; NZ-105; Serefodipine Hydrochloride. Cyclic 2,2-dimethyltrimethylene ester of 2-(*N*-benzylanilino)ethyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-5-phosphononicontinate hydrochloride .

Эфонидипина Гидрохлорид

$C_{34}H_{38}N_3O_7P.HCl$ = 668.1.

CAS — 111011-63-3 (efonidipine); 111011-53-1 (efonidipine hydrochloride).



(efonidipine)

Profile

Efonidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is used as the hydrochloride in the treatment of hypertension.

◊ References.

1. Tanaka H, Shigenobu K. Efonidipine hydrochloride: a dual blocker of L- and T-type Ca channels. *Cardiovasc Drug Rev* 2002; **20:** 81–92.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Landel.

Enalapril *(BAN, rINN)*

Enalapriili; Énalapril; Enalaprilum. *N*-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-L-proline.

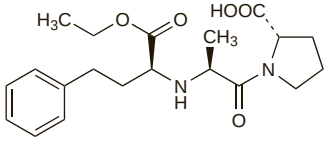
Эналаприл

$C_{20}H_{28}N_2O_5$ = 376.4.

CAS — 75847-73-3.

ATC — C09AA02.

ATC Vet — QC09AA02.



Enalapril Maleate *(BANM, USAN, rINNM)*

Enalapriilimaleaatti; Enalapril Maleat; Énalapril, maléate d'; Enalapril maleinát; Enalaprili maleas; Enalaprilio maleatas; Enalaprilmaleat; Enalapril-maleát; Maleato de enalapril; MK-421. *N*-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-L-proline hydrogen maleate.

Эналаприла Малеат

$C_{20}H_{28}N_2O_5.C_4H_4O_4$ = 492.5.

CAS — 76095-16-4.

ATC — C09AA02.

ATC Vet — QC09AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Enalapril Maleate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 1% solution in water has a pH of 2.4 to 2.9. Protect from light.
USP 31 (Enalapril Maleate). An off-white crystalline powder. Sparingly soluble in water; soluble in alcohol; freely soluble in dimethylformamide and in methyl alcohol; slightly soluble in semipolar organic solvents; practically insoluble in nonpolar organic solvents.

Stability. Enalapril has been reported[1,2] to be stable for at least 56 days in extemporaneously compounded oral liquids containing enalapril maleate 1 mg/mL in a number of vehicles.

1. Nahata MC, *et al.* Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1155–7.
2. Allen LV, Erickson MA. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1915–20.

Enalaprilat *(BAN, USAN, rINN)*

Énalaprilate; Énalaprilate dihydraté; Enalaprilatum; Enalaprilatum dihydricum; Enalaprilic acid; MK-422. *N*-{*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl}-L-proline dihydrate.

Эналаприлат

$C_{18}H_{24}N_2O_5.2H_2O$ = 384.4.

CAS — 76420-72-9 (anhydrous enalaprilat); 84680-54-6 (enalaprilat dihydrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Enalaprilat Dihydrate). A white or almost white, hygroscopic, crystalline powder. It exhibits pseudopolymorphism. Very slightly soluble or slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetonitrile. Store in airtight containers.
USP 31 (Enalaprilat). A white to nearly white, hygroscopic, crystalline powder. Soluble 1 in 200 of water, 1 in 40 of dimethylformamide, and 1 in 68 of methyl alcohol; very slightly soluble in alcohol, in acetone, and in hexane; practically insoluble in acetonitrile and in chloroform; slightly soluble in isopropyl alcohol.

Incompatibility. Enalaprilat was visually incompatible[1] with phenytoin sodium in sodium chloride 0.9%, producing a crystalline precipitate; there was also some visual evidence of incompatibility when mixed with amphotericin B in glucose 5%.

1. Thompson DF, *et al.* Visual compatibility of enalaprilat with selected intravenous medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2530–1.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Incidence of adverse effects. Postmarketing surveillance for enalapril was carried out by prescription-event monitoring of 12 543 patients.[1] There were 374 skin events including facial oedema or angioedema in 29 (leading to withdrawal of treatment in 10), 15 cases of photosensitivity, and urticaria in 32 (leading to withdrawal in 5). Syncope and dizziness occurred in 155 and 483 patients respectively, sometimes in association with hypotension. Hypotension occurred in 218 patients, 71 in the first month. Treatment was stopped in 121 patients with hypotension, and dosage reduced in 36. Other adverse effects reported included headache in 310 patients, paraesthesias in 126, taste disturbances in 25, conjunctivitis in 67, tachycardia in 194, cough in 360, renal failure in 82, muscle cramp in 96, diarrhoea in 236, and nausea and vomiting in 326. Of 1098 deaths only 10, due to renal failure, were thought possibly related to enalapril therapy. Dysgeusia and skin reactions appeared to be less common than has been reported for captopril, but precise comparisons were difficult; the range of adverse effects was similar.[2]

Deafness was a possible side-effect of enalapril noted earlier;[2] it was reported in 19 of the 12 543 patients monitored, but only while they were taking enalapril, there being no record of deafness after treatment stopped.

For further reference to some of these adverse effects, see under ACE Inhibitors, p.1193.

1. Inman WHW, *et al.* Postmarketing surveillance of enalapril I: results of prescription-event monitoring. *BMJ* 1988; **297:** 826–9.
2. Inman WHW, Rawson NSB. Deafness with enalapril and prescription event monitoring. *Lancet* 1987; **i:** 872.

Breast feeding. After a single dose of enalapril 20 mg in 5 women enalaprilat was detected[1] in breast milk in concentrations of 1 to 2.3 nanograms/mL (mean peak 1.72 nanograms/mL); enalapril was also present (mean peak 1.74 nanograms/mL). This compared with peak serum values of 39 to 112 nanograms/mL for enalaprilat and 92 to 151 nanograms/mL for enalapril. Another study[2] found no detectable enalaprilat in the milk of 3 women, while in a further woman[3] both enalapril and enalaprilat were detected, but the concentrations were low. Although enalapril and its metabolite are thus present in small amounts in breast milk it was calculated that the average total daily dose to the neonate would only be about 2 micrograms of enalaprilat.[1] The American Academy of Pediatrics[4] lists no reports of any clinical effect on the infant associated with the use of enalapril by breast-feeding mothers, and states that therefore it may be considered to be usually compatible with breast feeding.

1. Redman CWG, *et al.* The excretion of enalapril and enalaprilat in human breast milk. *Eur J Clin Pharmacol* 1990; **38:** 99.
2. Huttunen K, *et al.* Enalapril treatment of a nursing mother with slightly impaired renal function. *Clin Nephrol* 1989; **31:** 278.
3. Rush JE, *et al.* Comment. *Clin Nephrol* 1991; **35:** 234.
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 05/07/04)

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

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Enalapril acts as a prodrug of the diacid enalaprilat, its active form, which is poorly absorbed orally. About 60% of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about 1 hour. Enalapril is extensively hydrolysed in the liver to enalaprilat; peak plasma concentrations of enalaprilat are achieved 3 to 4 hours after an oral dose of enalapril. Enalaprilat is 50 to 60% bound to plasma proteins. After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged drug, with the urinary route predominating; more than 90% of an intravenous dose of enalaprilat is excreted in the urine. The elimination of enalaprilat is multiphasic but the effective half-life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function. Enalaprilat is removed by haemodialysis and by peritoneal dialysis.

◊ References.

1. MacFadyen RJ, *et al.* Enalapril clinical pharmacokinetics and pharmacokinetic-pharmacodynamic relationships: an overview. *Clin Pharmacokinet* 1993; **25:** 274–82.
2. Wells T, *et al.* The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; **41:** 1064–74.

Renal impairment. Comparison of the pharmacokinetics of enalapril in 6 diabetics with persistent proteinuria and glomerular filtration rates (GFR) of 44.1 to 58.4 mL/minute with those in 8 age-matched controls showed that in the diabetic group the peak serum concentration of enalaprilat was higher, the time to peak concentration longer, renal clearance lower, and the areas under the concentration/time curve greater than in controls.[1] Renal clearance of enalaprilat in the diabetics ranged from 56 to 66 mL/minute compared with 105 to 133 mL/minute in controls; clearance correlated with GFR.

1. Baba T, *et al.* Enalapril pharmacokinetics in diabetic patients. *Lancet* 1989; **i:** 226–7.

Uses and Administration

Enalapril is an ACE inhibitor (p.1193) used in the treatment of hypertension (p.1171) and heart failure (p.1165). It may also be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in patients with left ventricular dysfunction to reduce the incidence of coronary ischaemic events, including myocardial infarction (p.1175).

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6 hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the treatment of **hypertension**, an initial oral dose of 5 mg of enalapril maleate daily may be given. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be given to patients with renal impairment or to those who are receiving a *diuretic*; if possible, the diuretic should be