Preparations

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

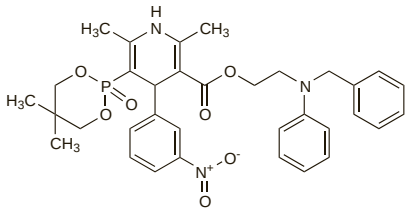
Efonidipine Hydrochloride *(rINNM)*

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.

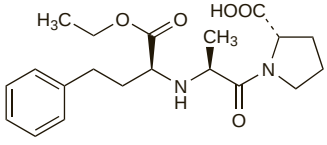
Эналаприл

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