withdrawn 2 or 3 days before enalapril is started and resumed later if necessary. The usual maintenance dose is 10 to 20 mg given once daily, although doses of up to 40 mg daily may be required in severe hypertension. It may be given in 2 divided doses if control is inadequate with a single dose.

When oral therapy of hypertension is impractical enalaprilat may be given in a dose of 1.25 mg by slow intravenous injection or infusion over at least 5 minutes, repeated every 6 hours if necessary; the initial dose should be halved in patients with renal impairment (creatinine clearance less than 30 mL/minute) or those who are receiving a diuretic.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. In patients with heart failure or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

Administration in children. Enalapril may be used in the management of hypertension in children.[1] The initial dose is 80 micrograms/kg once daily, with a maximum of 5 mg, adjusted according to response. Alternatively, children weighing 20 to below 50 kg may be given an initial dose of 2.5 mg once daily, increased to a maximum of 20 mg daily, while children weighing 50 kg or over may be given an initial dose of 5 mg once daily, increased to a maximum of 40 mg daily. Doses above 580 micrograms/kg or 40 mg daily have not been studied.

Enalapril has also been given to infants with severe heart failure in doses of 100 to 500 micrograms/kg daily as an oral suspension produced by suspending a crushed tablet in water.[2] In this study one infant, with severe myocarditis, developed hypotension and the drug had to be withdrawn; the remaining 7 showed clinical improvement on a mean enalapril dose of 260 micrograms/kg daily and were able markedly to reduce the dose of concomitant diuretic required. Another study in 10 infants found that enalapril was less bioavailable and probably had a shorter duration of action in infants than in adults, and that doses of 80 micrograms/kg daily were inadequate in the treatment of infant heart failure.[3] A larger study in 63 infants and children (median age 5.4 months) with heart failure found enalapril 360 micrograms/kg daily to be of benefit, whereas there was no improvement with a lower dose of 240 micrograms/kg daily.[4]

1. Wells T, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol* 2002; **42:** 870–80.
2. Frenneaux M, *et al.* Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989; **64:** 219–23.
3. Lloyd TR, *et al.* Orally administered enalapril for infants with congestive heart failure: a dose-finding study. *J Pediatr* 1989; **114:** 650–4.
4. Leversha AM, *et al.* Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994; **70:** 35–9.

Preparations

BP 2008: Enalapril Tablets;
USP 31: Enalapril Maleate and Hydrochlorothiazide Tablets; Enalapril Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baypril; Defluin; Dentromin; Ecaprilat; Enalafel; Enalapoten; Enaldun; Enatral; Enatrial; Eritril; Fabotensil; Gadopril; Glioten; Hipertan; Kinfil; Lotrial; Maxen; Nalapril; Presi Regul; Priltenk; Renitec; Sulocten; Tencas; Vapresan; Vasopril; ***Austral.:*** Alphapril; Amprace; Auspril; Enahexal; Enalabell; Renitec; ***Austria:*** Alapril; Enac; Enalanorm; Enapril; Enaran; Enatyrol†; Mepril; Renistad; Renitec; ***Belg.:*** Renitec; ***Braz.:*** Angiopril†; Atens; Blootec†; Enalabal; Enalamed; Enalaplex†; Enalatec; Enalil; Enalprin†; Enaprotec†; Enatec†; Enaton†; Eupressin; Glioten; Hipertin†; Lowpress†; Maleapril†; Multipressim; Nalaprix†; Neolapril†; Pressel; Pressotec; Prodopressin; Pryltec; Renalapril; Renipress; Renitec; Renopress†; Sanvapress; Sifpryl†; Vasopril; ***Canad.:*** Vasotec; ***Chile:*** Bajaten; Enalten; Esalfon; Glioten; Grifopril; Hiperson; Hipoartel†; Lotrial; Vasolat†; ***Cz.:*** Acetensil†; Berlipril; E-Cor†; Ednyt; Enap; Enapirex†; Enapril; Invoril; Renitec; ***Denm.:*** Acerent†; Alacor†; Corodil; Enacodan; Enadil†; Renitec; ***Fin.:*** Enaloc†; Enapress†; Linatil; Renitec; ***Fr.:*** Renitec; ***Ger.:*** Benalapril; Corvo; Ena; Ena-Puren; Enabeta; enadura; Enahexal; Enal†; Enalagamma; EnaLich; Enalind†; Jutaxan; Pres; Xanef; ***Gr.:*** Agioten; Analept; Antiprex; Enxetilan; Gnostocardin; Kaparlon-S; Kontic†; Leovinezal; Megapress; Octorax; Ofnifenil; Protal†; Rablas; Renitec; Stadelant; Supotron; Ulticadex; Virfen; Vitobel†; ***Hong Kong:*** Anapril; Danssan; Enaldun; Lapril; Renitec; ***Hung.:*** Acepril; Berlipril; Ednyt; Enap; Enapril; Invoril; Renapril; Renitec; ***India:*** BQL; Dilvas; Ena; EnAce; Envas; Nuril; ***Indon.:*** Meipril; Renacardon; Tenace; ***Irl.:*** Ednyt†; Enap; Innomel†; Innovace; ***Israel:*** Convertin; Enaladex; ***Ital.:*** Converten; Enapren; Naprilene; Silverit; ***Malaysia:*** Acetec; Enapril; Invoril; Renitec; Zynace†; ***Mex.:*** Adytenn; Albec; Apo-Pyl; Bimetdad; Bionafil; Blocatril; EK-3; Enaladil; Enoval; Euronal; Feliberal; Glioten; Imotoran; Kenopril†; Lipraken; Nalabest; Norpril; Palane; Pulsol; Quimalan†; Ralser; Renitec; Vexotil; ***Neth.:*** Renitec; ***Norw.:*** Linatil†; Renitec; ***NZ:*** Enahexal; Renitec; ***Philipp.:*** Acebitor; Hipertal; Hypace; Naprilate; Renitec; Stadenace; Vasopress; ***Pol.:*** Benalapril; Ednyt; Enap; Enarenal; Enazil; Epril; Mapryl; ***Port.:*** Balpril; Cetampril; Chipil; Denapril; Diasistol; Enapress; Hipobar; Hipten†; Malen†; Prilan; Renipril†; Renitec; Tensazol; ***Rus.:*** Bagopril (Багоприл); Berlipril (Берлиприл); Ednyt (Эднит); Enafarm (Энафарм); Enam (Энам); Enap (Энап); Enarenal (Энаренал); Enazil (Эназил)†; Envas (Энвас); Invoril (Инворил); Kalpiren (Кальпирен); Myopril (Миоприл); Renipril (Ренприл); Renitec (Ренитек); Vasopren (Вазопрен)†; ***S.Afr.:*** Alapren; Ciplatec; Enap; Hypace†; Pharmapress; Renitec; ***Singapore:*** Anapril; Corprilor; Daren†; Enap; Enaril; Invoril; Korandil; Renaton†; Renitec; ***Spain:*** Acetensil; Baripril; Bitensil; Clipto; Controlvas; Corprilor; Crinoren; Dabonal; Ditensor; Herten; Hipoartel; Iecatec; Insup; Nacor†; Naprilene; Neotensin; Pressitan; Reca; Renitec; ***Swed.:*** Linatil; Renitec; ***Switz.:*** Acepril; Elpradil; ena-basan†; Enasifar†; Enatec; Epril; Reniten; Vasocor; ***Thai.:*** Anapril; Enam; Enapril; Enaril; Envas; Iecatec†; Invoril; Istopril; Korandil; Lapril; Nalopril; Naritec; Renitec; Unaril; ***Turk.:*** Enalap; Enapril; Konveril; Renitec; Vasolapril; ***UAE:*** Naprapril; ***UK:*** Enacard†; Innovace; Pralenal†; ***USA:*** Vasotec; ***Venez.:*** Cosil; Dinid; Enalaprin†; Enam†; Enaprival†; Eneca; Fibrosan; Hiperpril; Lapril†; Prilace; Redopril; Reminal; Renitec; Tesoren†.

Multi-ingredient: *Arg.:* Co-Renitec; Defluin Plus; Fabotensil D; Gadopril D; Glioten zide; Kinfil D; Lotrial D; Lotrix†; Maxen D; Nikion†; Presi Regul D; Tencas D; Vapresan Diur; ***Austral.:*** Renitec Plus; ***Austria:*** Co-Enac; Co-Enalapril; Co-Enaran; Co-Enatyrol†; Co-Mepril; Co-Renitec; Corenistad; Enacostad†; Enalapril Comp; Enalapril/HCT; Renitec Plus; Synerpril; ***Belg.:*** Co-Enalapril; Co-Renitec; ***Braz.:*** Atens H; Atmos; Co-Enalil; Co-Enaprotec†; Co-Pressoless; Co-Pressotec; Co-Renitec; Duopril; Enatec F†; Eupressin H; Gliotenzide; Malena HCT; Pryltec-H; Sinergen; Vasopril Plus; ***Canad.:*** Vaseretic; ***Chile:*** Bajaten D; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hiperson-D; Hipoartel H†; Lotrial D; Normaten; Normaten Plus; ***Cz.:*** Enap-H; Enap-HL; ***Denm.:*** Co-Renitec†; Corodil Comp; Enacozid; Synerpril; ***Fin.:*** Enalapril Comp; Enaloc Comp†; Linatil Comp; Renitec Comp; Renitec Plus; ***Fr.:*** Co-Renitec; ***Ger.:*** Benalapril Plus; Corvo HCT; Enabeta comp; Enadura Plus; Enahexal comp; Enala-Q comp; Enalagamma HCT; Enalapril Comp; Enalapril HCT; Enalapril plus; Enalapril-saar Plus; EnaLich comp; Enaplus; Eneas; Pres plus; Renacor; ***Gr.:*** Bumeftyl; Co-Renitec; Coredopril; Eneas; Enit; Iperton; Modinexil†; Nolarmin; Penopril; Protal complex; Savosan; Siberian; ***Hong Kong:*** Co-Renitec; ***Hung.:*** Acepril PlusZ; Co-Enalapril; Co-Renitec; Ednyt HCT; Ednyt Plus; Enalapril Hexal Plus; Enalapril-HCT; Enap-HL; Renapril Plus; Renitec Plus; ***India:*** Dilvas AM; EnAce-D; Invozide; ***Indon.:*** Tenazide; ***Irl.:*** Innozide; ***Israel:*** Naprizide; ***Ital.:*** Acesistem; Condiuren; Gentipress; Neoprex; Sinertec; Vasoretic; ***Mex.:*** Co-Renitec; Gliotenzide; ***Neth.:*** Co-Renitec; Enacostad†; Renitec Plus; ***Norw.:*** Enalapril Comp; Renitec Comp; ***NZ:*** Co-Renitec; ***Philipp.:*** Co-Renitec; ***Pol.:*** Enap H; Enap HL; ***Port.:*** Enatia; Eneas; Enit; Laprilen; Neodur; Norpramin; Renidur; Renipril Plus; ***Rus.:*** Co-Renitec (Ко-Ренитек); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Enzix (Энзикс); Renipril HT (Ренприл ГТ); ***S.Afr.:*** Co-Renitec; Enap-Co; Pharmapress Co; ***Singapore:*** Co-Renitec; Enap-HL; Gliotenzide; ***Spain:*** Acediur; Acetensil Plus; Baripril Diu; Bitensil Diu; Co-Renitec; Crinoretic; Dabonal Plus; Ditenside; Eneas; Enit; Hipoartel Plus; Neotensin Diu; Pressitan Plus; Renitecmax; Vipres; Zorail; ***Swed.:*** Enalapril Comp; Linatil Comp; Renitec Comp; Synerpril; ***Switz.:*** Co-Acepril; Co-Enalapril; Co-Enatec; Co-Epril; Co-Reniten; Co-Vasocor; Elpradil HCT; Epril Plus; Reniten Plus; ***Turk.:*** Konveril Plus; ***UK:*** Innozide; ***USA:*** Lexxel; Teczem; Vaseretic; ***Venez.:*** Co-Renitec; Duopres; Priretic†; Reminalet.

Endralazine Mesilate *(BANM, rINNM)*

BQ-22-708; Compound 22-708; Endralazine, Mésilate d'; Endralazine Mesylate *(USAN)*; Endralazini Mesilas; Mesilato de endralazina. 6-Benzoyl-5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazin-3-ylhydrazone monomethanesulfonate.

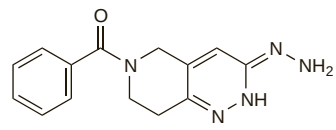
Эндралазина Мезилат

$C_{14}H_{15}N_5O,CH_4O_3S$ = 365.4.

CAS — 39715-02-1 (endralazine); 65322-72-7 (endralazine mesilate).

ATC — C02DB03.

ATC Vet — QC02DB03.



(endralazine)

Profile

Endralazine is a vasodilator with properties similar to those of hydralazine (p.1305). It has been used as the mesilate in the management of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Miretilan†.

Enoxaparin Sodium *(BAN, USAN, rINN)*

Enoksapariininatrium; Enoksaparin Sodyum; Enoksaparino natrio druska; Enoksaparyna sodowa; Enoxaparin sodná sůl; Enoxaparina sódica; Énoxaparine sodique; Enoxaparinnatrium; Enoxaparinnátrium; Enoxaparinum natricum; PK-10169; RP-54563.

Эноксапарин Натрий

CAS — 9041-08-1; 679809-58-6.

ATC — B01AB05.

ATC Vet — QB01AB05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Enoxaparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain; 15 to 25% of the components have a 1,6-anhydro structure at the reducing end of their chain. The mass-average molecular mass ranges between 3800 and 5000 with a characteristic value of about 4500. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 90 units and not more than 125 units of anti-factor Xa activity per mg, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20 units and not more than 35 units per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7.

USP 31 (Enoxaparin Sodium). The sodium salt of a depolymerised heparin obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. About 20% of the components contain a 1,6-anhydro derivative on the reducing end of the chain. The mass-average molecular weight of enoxaparin sodium is 4,500, the range being between 3,800 and 5,000.

It has a potency of not less than 90 units and not more than 125 units of anti-factor Xa per mg, and not less than 20 units and not more than 35 units of anti-factor IIa per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7. Store in airtight containers at a temperature below 40°.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329. Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring.

Severe bleeding with enoxaparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of 1 mg (100 units) of enoxaparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Enoxaparin is rapidly and almost completely absorbed after subcutaneous injection with a bioavailability of about 100%. Peak plasma activity is reached within 1 to 5 hours. The elimination half-life is about 4 to 5 hours but anti-factor Xa activity persists for up to 24 hours after a 40-mg dose. Elimination is prolonged in patients with renal impairment. Enoxaparin is metabolised in the liver and excreted in the urine, as unchanged drug and metabolites.

◊ References.

1. Hulot JS, *et al.* Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit* 2004; **26:** 305–10.
2. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J* 2004; **148:** 582–9.

Uses and Administration

Enoxaparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p.1157) and in ST-elevation myocardial infarction (p.1175).

In the *prophylaxis* of **venous thromboembolism** during surgical procedures, enoxaparin sodium is given by subcutaneous injection; treatment is continued for 7 to 10 days or until the patient is ambulant.

- Patients at low to moderate risk are given 20 mg (2000 units) once daily with the first dose about 2 hours pre-operatively.
- In patients at high risk, such as those undergoing orthopaedic surgery, the dose should be increased to 40 mg (4000 units) once daily with the initial dose given about 12 hours before the procedure. Alternatively, a dose of 30 mg (3000 units) may be given subcutaneously twice daily, starting within 12 to 24