withdrawn 2 or 3 days before enalapril is started and resumed later if necessary.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tablet in water.[2] In this study one infant, with severe myocarditis, developed hypotension and the drug had to be withdrawn; the remaining 7 showed clinical improvement on a mean enalapril dose of 260 micrograms/kg daily and were able markedly to reduce the dose of concomitant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.

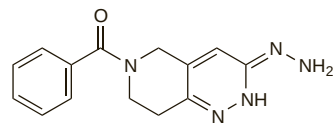
Эндралазина Мезилат

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

hours after operation. After hip replacement surgery, enoxaparin sodium may be continued in a dose of 40 mg (4000 units) once daily for a further 3 weeks.

- For the prophylaxis of thromboembolism in immobilised medical patients, the dose is 40 mg (4000 units) once daily for at least 6 days; treatment should be continued until the patient is fully ambulant, up to a maximum of 14 days.

For the *treatment* of deep-vein thrombosis enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours, or 1.5 mg/kg (150 units/kg) once daily, for at least 5 days and until oral anticoagulation is established.

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, enoxaparin sodium 1 mg/kg (100 units/kg) is introduced into the arterial line of the circuit at the beginning of the dialysis session. A further dose of 0.5 to 1 mg/kg (50 to 100 units/kg) may be given if required. The dose should be reduced in patients at high risk of haemorrhage.

In the management of **unstable angina**, enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours. Treatment is usually continued for 2 to 8 days.

In acute ST-elevation **myocardial infarction** the initial dose of enoxaparin is 30 mg (3000 units) intravenously, with a subcutaneous dose of 1 mg/kg (100 units/kg) given at the same time. Further doses of 1 mg/kg (100 units/kg) should be given subcutaneously every 12 hours for 8 days or until hospital discharge. The first 2 subcutaneous doses should not exceed 100 mg (10 000 units) each. For patients who undergo a percutaneous coronary intervention, an additional intravenous dose of 300 micrograms/kg (30 units/kg) should be given at the time of the procedure if the last subcutaneous dose was given more than 8 hours previously. Patients aged 75 years and older with acute myocardial infarction should be given subcutaneous doses only; the recommended dose is 750 micrograms/kg (75 units/kg) every 12 hours, with a maximum of 75 mg (7500 units) for each of the first 2 doses.

The dose of enoxaparin sodium should be reduced in patients with severe renal impairment (see below).

◊ References.

1. Noble S, *et al.* Enoxaparin: a reappraisal of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disease. *Drugs* 1995; **49:** 388–410.
2. Noble S, Spencer CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. *Drugs* 1998; **56:** 259–72.
3. Harvey DM, Offord RH. Management of venous and cardiovascular thrombosis: enoxaparin. *Hosp Med* 2000; **61:** 628–36.
4. Ibbotson T, Goa KL. Enoxaparin: an update of its clinical use in the management of acute coronary syndromes. *Drugs* 2002; **62:** 1407–31.
5. Fareed J, *et al.* Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. *Clin Pharmacokinet* 2003; **42:** 1043–57.
6. Siddiqui MAA, Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; **65:** 1025–36.
7. Carter NJ, *et al.* Enoxaparin: a review of its use in ST-segment elevation myocardial infarction. *Drugs* 2008; **68:** 691–710.

Administration in infants and children. Increasing numbers of infants and children are given anticoagulants for the management of thromboembolism. Few controlled studies have been carried out in this age group and recommendations for therapy have generally been adapted from adult guidelines. Low-molecular-weight heparins may have a number of advantages in children. Enoxaparin has been used for the prophylaxis[1] of thromboembolism in children including neonates, and for treatment in children including neonates[1-3] and preterm infants.[1,3-5] Younger children may require a higher dose than older children. US guidelines recommend the following doses for *treatment*[6] of thromboembolism:

- under 2 months of age: 1.5 mg/kg (150 units/kg) every 12 hours
- over 2 months of age: 1 mg/kg (100 units/kg) every 12 hours

Doses for *prophylaxis*[6] are:

- under 2 months of age: 750 micrograms/kg (75 units/kg) every 12 hours
- over 2 months of age: 500 micrograms/kg (50 units/kg) every 12 hours

Similar doses are recommended in the UK by the *BNFC*, although it specifies slightly modified doses in neonates, in whom it recommends 1.5 to 2 mg/kg twice daily for *treatment* and 750 micrograms/kg twice daily for *prophylaxis*.

1. Dix D, *et al.* The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000; **136:** 439–45.
2. Massicotte P, *et al.* Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996; **128:** 313–18.
3. Streif W, *et al.* Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F365–F370.
4. Dunaway KK, *et al.* Use of enoxaparin in a preterm infant. *Ann Pharmacother* 2000; **34:** 1410–13.
5. Michaels LA, *et al.* Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics* 2004; **114:** 703–7.
6. 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.

Administration in renal impairment. Careful monitoring is required when enoxaparin sodium is given to patients with mild to moderate renal impairment.[1] In severe renal impairment (creatinine clearance less than 30 mL/minute) the dose should be reduced. For prophylaxis of venous thromboembolism, UK licensed product information recommends a dose of 20 mg (2000 units) subcutaneously once daily whereas US licensed product information recommends a subcutaneous dose of 30 mg (3000 units) once daily. For treatment of venous thromboembolism, unstable angina, or acute myocardial infarction in patients aged 75 years or older, a dose of 1 mg/kg (100 units/kg) subcutaneously once daily is advised; patients under 75 years with myocardial infarction should additionally be given a single intravenous dose of 30 mg (3000 units) with the first subcutaneous dose. However, the adequacy of a once-daily dose in patients with acute coronary syndromes has been questioned and alternative dosage regimens have been suggested.2,3

1. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. *Drug Safety* 2007; **30:** 991–4.
2. Hulot J-S, *et al.* Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther* 2005; **77:** 542–52.
3. Green B, *et al.* Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; **59:** 281–90.

Preparations

USP 31: Enoxaparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Clexane; Dilutol; ***Austral.:*** Clexane; ***Austria:*** Lovenox; ***Belg.:*** Clexane; ***Braz.:*** Clexane; Cutenox†; Dripanina; ***Canad.:*** Lovenox; ***Chile:*** Clexane; Nu-Rox; ***Cz.:*** Clexane; ***Denm.:*** Klexane; ***Fin.:*** Klexane; ***Fr.:*** Lovenox; ***Ger.:*** Clexane; ***Gr.:*** Clexane; ***Hong Kong:*** Clexane; ***Hung.:*** Clexane; ***India:*** Clexane; ***Indon.:*** Lovenox; ***Irl.:*** Clexane; ***Israel:*** Clexane; ***Ital.:*** Clexane; ***Malaysia:*** Clexane; ***Mex.:*** Clexane; ***Neth.:*** Clexane; ***Norw.:*** Klexane; ***NZ:*** Clexane; ***Philipp.:*** Clexane; ***Pol.:*** Clexane; ***Port.:*** Klexane; Lovenox; ***Rus.:*** Clexane (Клексан); ***S.Afr.:*** Clexane; ***Singapore:*** Clexane; ***Spain:*** Clexane; Decipar; ***Swed.:*** Klexane; ***Switz.:*** Clexane; ***Thai.:*** Clexane; ***Turk.:*** Clexane; ***UK:*** Clexane; ***USA:*** Lovenox; ***Venez.:*** Clexane; Enoparin.

Multi-ingredient: ***Cz.:*** Clexane anti Xa-IU.

Enoximone *(BAN, USAN, rINN)*

Enoksimoni; Enoximon; Enoximona; Énoximone; Enoximonum; Fenoximone; MDL-17043; MDL-19438; RMI-17043; YMDL-17043. 4-Methyl-5-[4-(methylthio)benzoyl]-4-imidazolin-2-one.

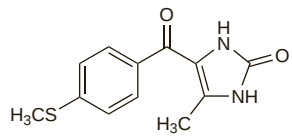
Эноксимон

$C_{12}H_{12}N_2O_2S$ = 248.3.

CAS — 77671-31-9.

ATC — C01CE03.

ATC Vet — QC01CE03.



Incompatibility. Crystal formation has occurred when enoximone injection was mixed in glass containers or syringes; the manufacturer recommends that only plastic containers or syringes are used for dilutions. The manufacturer also recommends that only sodium chloride 0.9% or water be used as diluents. Glucose solutions should not be used for dilution as crystal formation may occur.

Adverse Effects

Long-term oral treatment with enoximone has been reported to increase the mortality rate and enoximone is now only given intravenously for short-term use.

Enoximone may cause ventricular and supraventricular tachyarrhythmias, ectopic beats, and hypotension.

Adverse effects of enoximone affecting the gastrointestinal tract include diarrhoea, nausea, and vomiting. Other adverse effects include headache, insomnia, chills, oliguria, fever, urinary retention, and limb pain. There have been reports of thrombocytopenia and abnormal liver enzyme values.

Effects on the nervous system. Tonic-clonic convulsions have been reported[1] in a patient given enoximone 6 micrograms/kg per minute by intravenous infusion. The convulsions subsided when enoximone was stopped.

1. Appadurai I, *et al.* Convulsions induced by enoximone administered as a continuous intravenous infusion. *BMJ* 1990; **300:** 613–14.

Hyperosmolality. Hyperosmolality occurred in an infant during intravenous infusion of enoximone 20 micrograms/kg per minute. The probable cause was propylene glycol in the enoximone injection providing a dose of 2.4 mg/kg per minute.[1]

1. Huggon I, *et al.* Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990; **301:** 19–20.

Precautions

Enoximone should be used with caution in patients with hypertrophic cardiomyopathy or severe obstructive aortic or pulmonary valvular disease.

Blood pressure, heart rate, ECG, fluid and electrolyte status, and renal function should be monitored during therapy. Platelet count and liver enzyme values should also be monitored.

The injection has a high pH (about 12) and must be diluted before use (but see Incompatibility, above). Extravasation should be avoided.

Doses may need to be reduced in hepatic or renal impairment (see under Uses and Administration, below).

Pharmacokinetics

Although enoximone is absorbed from the gastrointestinal tract it is no longer given orally. The plasma elimination half-life varies widely; it may be about 1 to 4 hours in healthy subjects and about 3 to 8 hours in patients with heart failure, but longer times have been reported. Enoximone is about 85% bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites. After intravenous doses about 70% of a dose is excreted in the urine as metabolites and less than 1% as unchanged drug.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Uses and Administration

Enoximone is a phosphodiesterase inhibitor similar to amrinone (p.1215) with positive inotropic and vasodilator activity. It is given intravenously in the short-term management of heart failure. In some long-term studies it was given orally, but an increased mortality rate was reported.

The usual initial dose of enoximone by intravenous injection is 0.5 to 1.0 mg/kg given at a rate not greater than 12.5 mg/minute. This may be followed by doses of 500 micrograms/kg every 30 minutes until a satisfactory response is obtained or a total dose of 3 mg/kg has been given. Alternatively, the initial dose may be given as a continuous intravenous infusion in a dose of 90 micrograms/kg per minute over 10 to 30 minutes until the desired response is achieved.

For maintenance therapy the initial dose (up to a total of 3 mg/kg) may be repeated as required every 3 to 6 hours or a continuous or intermittent infusion may be given in a dose of 5 to 20 micrograms/kg per minute.

The total dose over 24 hours should not exceed 24 mg/kg.

Dosage may need to be reduced in patients with hepatic or renal impairment (see below).

◊ General references.

1. Vernon MW, *et al.* Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; **42:** 997–1017.

Administration in hepatic and renal impairment. The elimination half-life of enoximone after intravenous administra-