Dalteparin Sodium *(BAN, USAN, rINN)*

Daltepariininatrium; Dalteparin sodná sůl; Dalteparin Sodyum; Dalteparina sódica; Daltéparine sodique; Dalteparinnatrium; Dalteparin-nátrium; Dalteparino natrio druska; Dalteparinum natricum; Dalteparyna sodowa; Kabi-2165; Tedelparin Sodium.

Дальтепарин Натрий

CAS — 9041-08-1.

ATC — B01AB04.

ATC Vet — QB01AB04.

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

Ph. Eur. 6.2 (Dalteparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000. The mass percentage of chains lower than 3000 is not more than 13.0% and the mass percentage of chains higher than 8000 ranges between 15.0% and 25.0%. The degree of sulfation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 units and not more than 210 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

Units

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

Adverse Effects, Treatment, and Precautions

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

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

Interactions

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

Pharmacokinetics

Dalteparin is almost completely absorbed after subcutaneous doses, with a bioavailability of about 87%. Peak plasma activity is reached in about 4 hours. The terminal half-life is about 2 hours after intravenous injection and 3 to 5 hours after subcutaneous injection. Dalteparin is excreted via the kidneys and the half-life is prolonged in patients with renal impairment.

Uses and Administration

Dalteparin 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).

Dalteparin is given by subcutaneous or intravenous injection. Doses are expressed in terms of units of anti-factor Xa activity.

For *prophylaxis* of **venous thromboembolism** during surgical procedures, dalteparin is usually started pre-operatively.

- For patients at moderate risk of thrombosis 2500 units of dalteparin sodium are given by subcutaneous injection 1 to 2 hours before the procedure, followed by 2500 units once daily for 5 to 7 days or until the patient is fully ambulant.
- For patients at high risk, such as those undergoing orthopaedic surgery, 2500 units are given 1 to 2 hours before and 8 to 12 hours after the procedure followed by 5000 units daily. Alternatively, 5000 units may be given the evening before surgery followed by 5000 units each subsequent evening. This dosage may be continued for up to 5 weeks after hip replacement surgery.
- A further option in patients undergoing hip replacement surgery is to omit the pre-operative dose; treatment is begun with a dose of 2500 units given 4 to 8 hours postoperatively followed by 5000 units daily.
- For prophylaxis in medical patients, a dose of 5000 units once daily may be given for 14 days or longer.

In the *treatment* of established deep-vein thrombosis, pulmonary embolism, or both, dalteparin sodium is given subcutaneously in a dose of 200 units/kg daily. This may be given as a single dose or, in patients at higher risk of bleeding complications, in two divided doses. The maximum recommended dose is 18 000 units daily. Patients with symptomatic venous thromboembolism and cancer may be given 200 units/kg subcutaneously once daily for 30 days, followed by 150 units/kg once daily for up to 5 months.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** or **haemofiltration** in adults with chronic renal impairment an intravenous injection of dalteparin sodium 30 to 40 units/kg is followed by an intravenous infusion of 10 to 15 units/kg per hour. A single injection of 5000 units may be given for a haemodialysis or haemofiltration session lasting less than 4 hours. The dose of dalteparin sodium should be reduced in patients at high risk of bleeding complications or who are in acute renal failure; in such patients an intravenous injection of 5 to 10 units/kg is followed by an infusion of 4 to 5 units/kg per hour.

In the management of **unstable angina**, dalteparin sodium is given subcutaneously in a dose of 120 units/kg every 12 hours; the maximum dose is 10 000 units every 12 hours. Treatment is continued for 5 to 8 days and low-dose aspirin should also be given. For patients who require treatment for longer than 8 days while awaiting a revascularisation procedure, a dose of 5000 units (7500 units in men weighing 70 kg or over and women weighing 80 kg or over) may be given every 12 hours for up to 45 days until the procedure is performed.

◊ References.

1. Dunn CJ, Sorkin EM. Dalteparin sodium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs* 1996; **52:** 276–305.
2. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother* 1997; **31:** 192–203.
3. Dunn CJ, Jarvis B. Dalteparin: an update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2000; **60:** 203–37.
4. Pineo GF, Hull RD. Dalteparin: pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic diseases. *Eur J Med Res* 2004; **9:** 215–24.
5. Bick RL. Cancer-associated thrombosis: focus on extended therapy with dalteparin. *J Support Oncol* 2006; **4:** 115–20.
6. Linkins LA. Management of venous thromboembolism in patients with cancer: role of dalteparin. *Vasc Health Risk Manag* 2008; **4:** 279–87.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ligofragmin; ***Austral.:*** Fragmin; ***Austria:*** Fragmin; ***Belg.:*** Fragmin; ***Braz.:*** Fragmin; ***Canad.:*** Fragmin; ***Chile:*** Fragmin; ***Cz.:*** Fragmin; ***Denm.:*** Fragmin; ***Fin.:*** Fragmin; ***Fr.:*** Fragmine; ***Ger.:*** Fragmin; ***Gr.:*** Fragmin; ***Hong Kong:*** Fragmin; ***Hung.:*** Fragmin; ***Israel:*** Fragmin; ***Ital.:*** Fragmin; ***Mex.:*** Fragmin†; ***Neth.:*** Fragmin; ***Norw.:*** Fragmin; ***NZ:*** Fragmin; ***Philipp.:*** Fragmin; ***Pol.:*** Fragmin; ***Port.:*** Fragmin; ***Rus.:*** Fragmin (Фрагмин); ***S.Afr.:*** Fragmin; ***Singapore:*** Fragmin; ***Spain:*** Boxol†; Fragmin; ***Swed.:*** Fragmin; ***Switz.:*** Fragmin; ***Turk.:*** Fragmin; ***UK:*** Fragmin; ***USA:*** Fragmin; ***Venez.:*** Fragmin.

Danaparoid Sodium *(BAN, USAN, rINN)*

Danaparoid sodná sůl; Danaparoid sodowy; Danaparoide sódico; Danaparoïde sodique; Danaparoidum natricum; Lomoparan; Org-10172.

Данапароид Натрий

CAS — 83513-48-8.

ATC — B01AB09.

ATC Vet — QB01AB09.

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

Ph. Eur. 6.2 (Danaparoid Sodium). A preparation containing the sodium salts of a mixture of sulfated glycosaminoglycans present in porcine tissues. It is prepared from the intestinal mucosa of pigs and the major constituents are suleparoid (heparan sulfate) (p.1406) and dermatan sulfate (p.1256). It has a potency of 11.0 to 17.0 anti-factor Xa units per milligram, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Adverse Effects and Treatment

Haemorrhage may occur after use of danaparoid sodium, although there is a possible decreased risk of bleeding complications compared with heparin. Liver enzymes may be transiently elevated. Other adverse effects include hypersensitivity reactions, thrombocytopenia, and pain at the site of injection.

Protamine sulfate only partially neutralises the anticoagulant effect of danaparoid sodium and cannot be relied on to reverse bleeding associated with overdosage.

Precautions

As for Heparin, p.1303.

Danaparoid sodium should not be given to patients who have developed thrombocytopenia with heparin if they show cross-reactivity in an *in-vitro* test.

Pharmacokinetics

After subcutaneous dosage danaparoid sodium is well absorbed and peak anti-factor Xa activity is reached in about 4 to 5 hours. The elimination half-lives of anti-factor Xa and anti-factor IIa (antithrombin) activities are about 25 and 7 hours, respectively. Danaparoid sodium is excreted in the urine.

Uses and Administration

Danaparoid sodium is a low-molecular-weight heparinoid. It is an anticoagulant and, like heparin (p.1303), enhances the action of antithrombin III. Like low-molecular-weight heparins (p.1329) it has a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin, but is reported to be a much more selective inhibitor of factor Xa than the low-molecular-weight heparins. It was therefore hoped that danaparoid might be associated with a low incidence of bleeding complications, although this has not been established.

Danaparoid sodium is used in the prophylaxis of venous thromboembolism (p.1189) in patients undergoing surgery. It may be used as an anticoagulant for prophylaxis or treatment in patients with heparin-induced thrombocytopenia providing there is no cross-reactivity. Danaparoid has been investigated in acute ischaemic stroke.

Doses of danaparoid sodium are expressed in terms of units of anti-factor Xa activity. In the prophylaxis of venous thromboembolism it is given by subcutaneous injection in a dose of 750 units twice daily for 7 to 10 days. The first dose should be given 1 to 4 hours before surgery.

For patients with heparin-induced thrombocytopenia requiring anticoagulation, danaparoid sodium is given intravenously. The initial bolus dose is 2500 units (or 1250 units for patients weighing less than 55 kg, or 3750 units for patients weighing more than 90 kg) followed by an infusion of 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days. Monitoring of plasma anti-factor Xa activity is recommended for patients with renal impairment, or those weighing more than 90 kg.

◊ References.

1. Skoutakis VA. Danaparoid in the prevention of thromboembolic complications. *Ann Pharmacother* 1997; **31:** 876–87.
2. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; **54:** 903–24.
3. Ibbotson T, Perry CM. Danaparoid: a review of its use in thromboembolic and coagulation disorders. *Drugs* 2002; **62:** 2283–2314.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Orgaran; ***Austria:*** Orgaran; ***Belg.:*** Orgaran; ***Canad.:*** Orgaran; ***Fr.:*** Orgaran; ***Ger.:*** Orgaran; ***Gr.:*** Orgaran; ***Neth.:*** Orgaran; ***NZ:*** Orgaran; ***Port.:*** Orgaran; ***Swed.:*** Orgaran; ***Switz.:*** Orgaran; ***UK:*** Orgaran; ***USA:*** Orgaran†.

Debrisoquine Sulfate *(rINNM)*

Debrisoquin Sulfate *(USAN)*; Débrisoquine, Sulfate de; Debrisoquine Sulphate *(BANM)*; Debrisoquini Sulfas; Isocaramidine Sulfate; Ro-5-3307/1; Sulfato de debrisoquina. 1,2,3,4-Tetrahydroisoquinoline-2-carboxamidine sulfate.

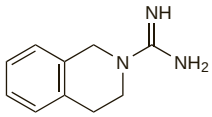
Дебризохина Сульфат

$(C_{10}H_{13}N_3)_2,H_2SO_4$ = 448.5.

CAS — 1131-64-2 (debrisoquine); 581-88-4 (debrisoquine sulfate).

ATC — C02CC04.

ATC Vet — QC02CC04.



(debrisoquine)

Pharmacopoeias. In *Br.*

BP 2008 (Debrisoquine Sulphate). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 3% solution in water has a pH of 5.3 to 6.8. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Guanethidine Monosulfate, p.1300.

Diarrhoea is rare with debrisoquine sulfate. Treatment should not be stopped abruptly as this may lead to rebound hypertension.

The metabolism of debrisoquine is subject to genetic polymorphism and non-metabolisers may show a marked response to doses that have little or no effect in metabolisers.

Interactions

As for Guanethidine Monosulfate, p.1300.

Pharmacokinetics

Debrisoquine is rapidly absorbed from the gastrointestinal tract. The major metabolite is 4-hydroxydebrisoquine; metabolism is subject to genetic polymorphism.

◊ A study[1] in 15 hypertensive patients and 4 healthy subjects indicated that debrisoquine undergoes pre-systemic metabolism to 4-hydroxydebrisoquine, but the mechanism appears to be saturable and increases in the dose of debrisoquine could therefore produce disproportionate decreases in blood pressure. The estimated half-life of elimination for debrisoquine and 4-hydroxydebrisoquine ranged from 11.5 to 26 hours and from 5.8 to 14.5 hours respectively.

1. Silas JH, *et al*. The disposition of debrisoquine in hypertensive patients. *Br J Clin Pharmacol* 1978; **5:** 27–34.

Genetic polymorphism. Debrisoquine, along with sparteine and a number of other drugs, is a substrate for the cytochrome P450 isoenzyme CYP2D6, a polymorphic enzyme coded by a gene mapped to chromosome 22. Patients homozygous for the mutant allele are termed *poor metabolisers* and express little or no active enzyme. The prevalence of the poor-metaboliser phenotype is about 5% in most Caucasian populations, while studies in other genetic groups have indicated a range of about 2 to 10% although in some groups, such as the Japanese, poor metabolisers have yet to be identified. Poor metabolisers of debrisoquine are unable to 4-hydroxylate the drug adequately to its inactive metabolite and are thus prone to excessive hypotension. Many other drugs are metabolised by the same enzyme, but the clinical consequences of polymorphism in patients taking them depends on the relative activity and toxicity of parent drug and metabolite, and the availability and relative importance of other routes of metabolism. Phenotype has been determined by giving a drug that is metabolised by this enzyme and assaying parent drug and metabolite in urine collected over a defined period of time, but DNA-based tests may represent a more convenient and safer alternative.

References.

1. Relling MV. Polymorphic drug metabolism. *Clin Pharm* 1989; **8:** 852–63.
2. Zanger UM, *et al*. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004; **369:** 23–37.

Uses and Administration

Debrisoquine is an antihypertensive with actions and uses similar to those of guanethidine (p.1300), but it causes less depletion of noradrenaline stores. When given orally, debrisoquine acts within about 4 to 10 hours and has effects lasting for 9 to 24 hours. It has been used in the management of hypertension (p.1171), but has largely been superseded by other drugs.

For reference to the use of debrisoquine in identifying metabolic phenotypes, see Genetic Polymorphism, above.

Defibrotide *(BAN, rINN)*

Defibrotida; Défibrotide; Defibrotidum.

Дефибротид

CAS — 83712-60-1.

ATC — B01AX01.

ATC Vet — QB01AX01.

Profile

Defibrotide consists of polydeoxyribonucleotides from bovine lung; the molecular weights range between 45 000 and 55 000. Preparations derived from porcine tissues and with a lower molecular weight range are also used. Defibrotide has antithrombotic and fibrinolytic properties, although its mechanism of action is uncertain; it appears to increase levels of prostaglandin E_2 and prostacyclin, to alter platelet activity, and to increase tissue plasminogen activator function at the same time as decreasing activity of tissue plasminogen activator inhibitor. It is used in the management of thromboembolic disorders. Oral and parenteral formulations have been used in doses of up to 800 mg daily.

Defibrotide is being investigated for use in the treatment of hepatic veno-occlusive disease and thrombotic thrombocytopenic purpura.

◊ References.

1. Palmer KJ, Goa KL. Defibrotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. *Drugs* 1993; **45:** 259–94.
2. Richardson PG, *et al*. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* 1998; **92:** 737–44.
3. Pogliani EM, *et al*. Defibrotide in recurrent thrombotic thrombocytopenic purpura. *Clin Appl Thromb Hemost* 2000; **6:** 69–70.
4. Chopra R, *et al*. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol* 2000; **111:** 1122–9.
5. Corti P, *et al*. Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 542–3.
6. Richardson PG, *et al*. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood* 2002; **100:** 4337–43.
7. Kornblum N, *et al*. Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. *Oligonucleotides* 2006; **16:** 105–14.
8. Ho VT, *et al*. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* 2008; **41:** 229–37.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Noravid; Prociclide.

Delapril Hydrochloride *(USAN, rINNM)*

Alindapril Hydrochloride; CV-3317; Délapril, Chlorhydrate de; Delaprili Hydrochloridum; Hidrocloruro de delapril; Indalapril Hydrochloride; REV-6000A. Ethyl (*S*)-2-{[(*S*)-1-(carboxymethyl-2-indanylcarbamoyl)ethyl]amino}-4-phenylbutyrate hydrochloride.

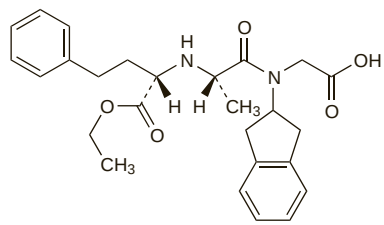
Делаприла Гидрохлорид

$C_{26}H_{32}N_2O_5$,HCl = 489.0.

CAS — 83435-66-9 (delapril); 83435-67-0 (delapril hydrochloride).

ATC — C09AA12.

ATC Vet — QC09AA12.



(delapril)

Profile

Delapril is an ACE inhibitor (p.1193). It is converted in the body to two metabolites to which it owes its activity. It is given orally as the hydrochloride in the treatment of hypertension (p.1171), in usual maintenance doses of 30 to 60 mg daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Delacard; ***Braz.:*** Delakete†; ***Gr.:*** Delacard; ***Ital.:*** Delaket; ***Jpn:*** Adecut; ***Malaysia:*** Cupressin†; ***Philipp.:*** Cupressin; ***Singapore:*** Cupressin; ***Spain:*** Beniod; Trinordiol; ***Thai.:*** Cupressin†.

Multi-ingredient: ***Austria:*** Delapride; ***Braz.:*** Hipertil; ***Gr.:*** Dinapres; Vivace; ***Ital.:*** Delapride; Dinapres.

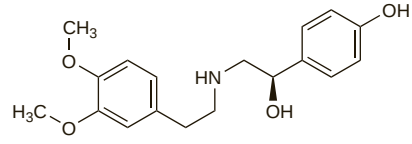
Denopamine *(rINN)*

Denopamina; Dénopamine; Denopaminum; TA-064. (–)-(*R*)-α-{[(3,4-Dimethoxyphenethyl)amino]methyl}-*p*-hydroxybenzyl alcohol.

Денопамин

$C_{18}H_{23}NO_4$ = 317.4.

CAS — 71771-90-9.



Profile

Denopamine is a sympathomimetic (p.1407) with predominantly beta-adrenergic activity selective to beta$_1$ receptors. It acts as a partial agonist (see Xamoterol, p.1433) and has been used for the treatment of heart failure.

Preparations

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

Dermatan Sulfate

Chondroitin Sulfate B; Dermatán, sulfato de; Dermatan Sulphate; LMW-DS (depolymerised dermatan sulfate); MF-701; OP-370 (depolymerised dermatan sulfate).

CAS — 24967-94-0 (dermatan sulfate).

ATC — B01AX04.

ATC Vet — QB01AX04.

Dermatan Sulfate Sodium

Chondroitin Sulfate B Sodium; Dermatan Sulphate Sodium.

CAS — 54328-33-5.

ATC — B01AX04.

ATC Vet — QB01AX04.

Profile

Dermatan sulfate is a naturally occurring glycosaminoglycan used as an anticoagulant for prophylaxis of venous thromboembolism (p.1189). It is given as the sodium salt in a dose of 100 to 300 mg daily by intramuscular injection. The dose may be increased to 300 mg twice daily in patients at high risk of thromboembolism, such as those undergoing major orthopaedic surgery.

Dermatan sulfate is a component of sulodexide (p.1406) and its sodium salt is a component of danaparoid sodium (p.1255).

Dermatan sulfate has been investigated for the treatment of venous thromboembolism, heparin-induced thrombocytopenia, and to prevent clotting during haemodialysis. Low-molecular-weight (depolymerised) dermatan sulfate has also been studied.

◊ References.

1. Dawes J, *et al*. The pharmacokinetics of dermatan sulphate MF701 in healthy human volunteers. *Br J Clin Pharmacol* 1991; **32:** 361–6.
2. Agnelli G, *et al*. Randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. *Thromb Haemost* 1992; **67:** 203–8.
3. Gianese F, *et al*. The pharmacokinetics and pharmacodynamics of dermatan sulphate MF701 during haemodialysis for chronic renal failure. *Br J Clin Pharmacol* 1993; **35:** 335–9.
4. Legnani C, *et al*. Acute and chronic effects of a new low molecular weight dermatan sulphate (Desmin 370) on blood coagulation and fibrinolysis in healthy subjects. *Eur J Clin Pharmacol* 1994; **47:** 247–52.
5. Miglioli M, *et al*. Bioavailability of Desmin, a low molecular weight dermatan sulfate, after subcutaneous administration to healthy volunteers. *Int J Clin Lab Res* 1997; **27:** 195–8.
6. Taliani MR *et al*. Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; **104:** 87–9.
7. Di Carlo V, *et al*. Dermatan sulphate for the prevention of post-operative venous thromboembolism in patients with cancer. *Thromb Haemost* 1999; **82:** 30–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Aclotan†; Mistral; ***Port.:*** Venorix.