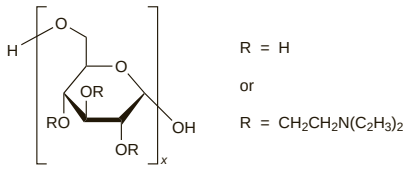
Colextran Hydrochloride *(rINNM)*

Colextran, Chlorhydrate de; Colextrani Hydrochloridum; DEAE-dextran Hydrochloride; Detaxtran Hydrochloride; Diethylaminoethyl-dextran Hydrochloride; Hidrocloruro de colextrán. Dextran 2-(diethylamino)ethyl ether hydrochloride.

Колекстрана Гидрохлорид

CAS — 9015-73-0 (colextran); 9064-91-9 (colextran hydrochloride).
ATC — C10AC03.
ATC Vet — QC10AC03.



Profile
Colextran hydrochloride, an anion-exchange resin that binds bile acids in the intestine, is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). It is given in a usual dose of 2 to 3 g daily orally in divided doses.

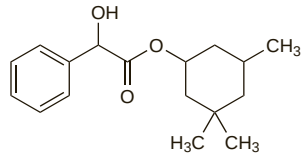
Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Pulsar; Rationale; ***Spain:*** Dexide.

Cyclandelate *(BAN, rINN)*

BS-572; Ciclandelato; Cyclandélate; Cyclandelatum; Cyklandelat; Syklandelaatti. 3,3,5-Trimethylcyclohexyl mandelate.

Циклanделат

$C_{17}H_{24}O_3$ = 276.4.
CAS — 456-59-7.
ATC — C04AX01.
ATC Vet — QC04AX01.



Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Cyclandelate). A white crystalline powder. M.p. about 58°. Practically insoluble in water; very soluble in alcohol, in acetonitrile, and in ether. Store in airtight containers below 40°, preferably between 15° and 30°. Protect from light.

Profile
Cyclandelate is a vasodilator used in the management of cerebrovascular (p.1165) and peripheral vascular disorders (p.1178). It is given orally in an initial dosage of up to 2 g daily in divided doses; a usual maintenance dose is 0.8 to 1.2 g daily.

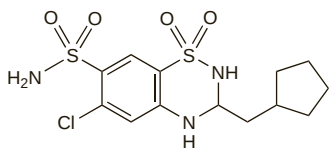
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Cyclospasmol†; ***Fin.:*** Cyclospasmol†; ***Fr.:*** Cyclergine†; Vascunormyl†; ***Ger.:*** Natil; Spasmocyclon†; ***India:*** Martispasmol†; ***Ital.:*** Ciclospasmol†; ***Neth.:*** Cyclospasmol; ***Port.:*** Cyclospasmol†; ***Swed.:*** Cyclomandol†.

Cyclopenthiazide *(BAN, USAN, rINN)* ⊗

Ciclopentiazida; Cyclopenthiaz.; Cyclopenthiazidum; Cyklopentiazid; NSC-107679; Su-8341; Syklopentiatsidi. 6-Chloro-3-cyclopentylmethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Циклопентиазид

$C_{13}H_{18}ClN_3O_4S_2$ = 379.9.
CAS — 742-20-1.
ATC — C03AA07.
ATC Vet — QC03AA07.



NOTE. Compounded preparations of cyclopenthiazide may be represented by the following names:

- Co-prenozide (*BAN*)—cyclopenthiazide 1 part and oxprenolol hydrochloride 640 parts (w/w).

Pharmacopoeias. In *Br.*
BP 2008 (Cyclopenthiazide). A white, odourless or almost odourless powder. Practically insoluble in water; soluble in alcohol and in acetone; practically insoluble in chloroform; very slightly soluble in ether.

Profile
Cyclopenthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis is induced in 1 to 3 hours after an oral dose, reaches a maximum in 4 to 8 hours, and lasts up to about 12 hours.

In the treatment of hypertension the usual dose is 250 to 500 micrograms daily either alone, or with other antihypertensives. In the treatment of oedema the usual initial dose is 250 to 500 micrograms daily; up to 1 mg daily may be given in heart failure but higher doses rarely achieve any further benefit. The dose should be reduced to the lowest effective dose for maintenance.

Porphyria. Cyclopenthiazide is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations
BP 2008: Cyclopenthiazide Tablets.

Proprietary Preparations (details are given in Part 3)
NZ: Navidrex†; ***UK:*** Navidrex.

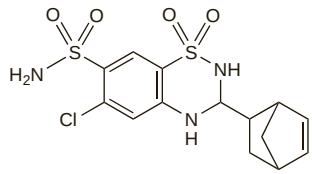
Multi-ingredient: ***Hong Kong:*** Navispare; ***S.Afr.:*** Lenurex-K; ***UK:*** Navispare; Trasidrex.

Cyclothiazide *(BAN, USAN, rINN)* ⊗

Ciclotiazida; Compound 35483; Cyclothiazidum; Cyklotiazid; MDi-193; Syklotiatsidi. 6-Chloro-3,4-dihydro-3-(norborn-5-en-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Циклотиазид

$C_{14}H_{16}ClN_3O_4S_2$ = 389.9.
CAS — 2259-96-3.
ATC — C03AA09.
ATC Vet — QC03AA09.



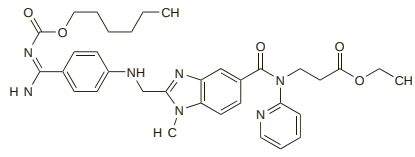
Profile
Cyclothiazide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used, usually in combination preparations, in the management of hypertension and oedema.

Dabigatran Etexilate *(rINN)*

BIBR-1048; BIBR-953 (dabigatran); Dabigatran Étexilate; Dabigatrán etexilato; Dabigatranum Etexilatum. Ethyl 3-({[2-({[4-({[(hexyloxy)carbonyl]amino}iminomethyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate.

Дабигатран Этексилат

$C_{34}H_{41}N_7O_5$ = 627.7.
CAS — 211914-51-1 (dabigatran); 211915-06-9 (dabigatran etexilate).
ATC — B01AE07.
ATC Vet — QB01AE07.



Adverse Effects and Treatment
The most common adverse effect with dabigatran is bleeding. Raised liver enzyme values have been reported but are uncommon. There is no antidote to dabigatran. If haemorrhagic complications occur treatment should be stopped; surgical haemostasis or transfusion of fresh frozen plasma may be considered.

Precautions
Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding. It should be used with caution in patients with hepatic or renal impairment and is contra-indicated if creatinine clearance is less than 30 mL/minute.

Interactions
Dabigatran should not be given with other drugs that affect coagulation, such as anticoagulants, thrombolytics, or antiplatelet drugs. It should be used with caution with NSAIDs since the risk of bleeding may be increased. Dabigatran is a substrate for the efflux transporter P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function; use of dabigatran with quinidine is contra-indicated, and the dose of dabigatran should be reduced in patients receiving amiodarone (see Uses and Administration, below).

Pharmacokinetics
When given orally, dabigatran etexilate is rapidly and completely hydrolysed to its active metabolite, dabigatran, by an esterase-catalysed reaction. The absolute oral bioavailability of dabigatran when given as dabigatran etexilate is about 6.5%. Peak plasma concentrations of dabigatran occur within 0.5 to 2 hours after an oral dose. Food delays the time to peak concentrations but the bioavailability is not affected. Dabigatran has low plasma-protein binding. It is metabolised to a limited extent to active acylglucuronide conjugates; about 85% of a dose is excreted in the urine, mainly as unchanged dabigatran. The terminal plasma half-life is about 12 to 17 hours. Dabigatran is removed by dialysis.

◊ Reviews.

1. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; **47:** 285–95.

Uses and Administration
Dabigatran is a direct thrombin inhibitor that is used for the prophylaxis of venous thromboembolism (p.1189) in patients undergoing elective orthopaedic surgery; it has also been investigated in other thromboembolic disorders.

Dabigatran is given orally as the mesilate of the prodrug dabigatran etexilate. The usual initial dose is the equivalent of 110 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 220 mg once daily; the dose should be reduced in the elderly and in patients with renal impairment (see below). Treatment should be continued for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

◊ References.

1. Stangier J, *et al.* The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007; **64:** 292–303.
2. Eriksson BI, *et al.* Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5:** 2178–85.
3. Eriksson BI, *et al.* RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007; **370:** 949–56.
4. Ezekowitz MD, *et al.* Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007; **100:** 1419–26.
5. Sanford M, Plosker GL. Dabigatran etexilate. *Drugs* 2008; **68:** 1699–1709.

Administration in the elderly. There is limited clinical experience with dabigatran in patients over the age of 75 years but plasma concentrations appear to be higher in older subjects[1] and dose reduction is recommended. UK licensed product information recommends an initial dose of 75 mg of dabigatran etexilate (as the mesilate) given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

1. Stangier J, *et al.* Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008; **47:** 47–59.

Administration in renal impairment. Dabigatran is excreted mainly by the kidneys but there is limited clinical experience with its use in renal impairment. It is contra-indicated in patients with creatinine clearance (CC) below 30 mL/minute. In patients with CC between 30 and 50 mL/minute the initial dose should be the equivalent of 75 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Pradaxa; ***UK:*** Pradaxa.

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†.