Profile
Cloridarol is a vasodilator that has been used in ischaemic heart disease.

Colesevelam Hydrochloride

(USAN, rINNM)

Colésévélam, Chlorhydrate de; Colesevelami Hydrochloridum; GT31-104HB; Hidrocloruro de colesevelam. Allylamine polymer with epichlorohydrin (1-chloro-2,3-epoxypropane), [6-(allylamino)hexyl]trimethylammonium chloride and *N*-allyldecylamine, hydrochloride.

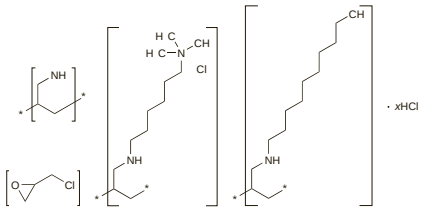
Колезевелама Гидрохлорид

$(C_3H_7N)_m(C_3H_5ClO)_n(C_{12}H_{27}ClN_2)_o(C_{13}H_{27}N)_p.xHCl$.

CAS — 182815-44-7.

ATC — C10AC04.

ATC Vet — QC10AC04.



Adverse Effects and Precautions
As for Colestyramine, p.1252.

Interactions
Colesevelam, like colestyramine (see p.1253), has the potential to interfere with the absorption of other drugs; those with a narrow therapeutic range should be given at least 1 hour before or 4 hours after colesevelam unless there is known to be no interaction.

◊ References.

1. Donovan JM, *et al.* Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000; **14:** 681–90.

Uses and Administration
Colesevelam hydrochloride is a nonabsorbable hydrogel. It binds bile acids in the intestine and has actions similar to those of colestyramine (p.1253). It is used for the treatment of hypercholesterolaemia (p.1169), particularly type IIa hyperlipoproteinaemia, either alone or with a statin. It may also be used as an adjunct to improve glycaemic control in type 2 diabetes mellitus (p.431). The usual oral dose is 3.75 g daily, as a single dose or in two divided doses, with meals. When used as monotherapy for hypercholesterolaemia, the dose may be increased to 4.375 g daily if required. When used with a statin, the dose is 2.5 to 3.75 g daily.

◊ References.

1. Davidson MH, *et al.* Colesevelam hydrochloride (Cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999; **159:** 1893–1900.
2. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother* 2001; **35:** 898–907.
3. Steinmetz KL. Colesevelam hydrochloride. *Am J Health-Syst Pharm* 2002; **59:** 932–9.
4. Zieve FJ, *et al.* Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *Clin Ther* 2007; **29:** 74–83.
5. Bays H, Jones PH. Colesevelam hydrochloride: reducing atherosclerotic coronary heart disease risk factors. *Vasc Health Risk Manag* 2007; **3:** 733–42.
6. Florentin M, *et al.* Colesevelam hydrochloride in clinical practice: a new approach in the treatment of hypercholesterolaemia. *Curr Med Res Opin* 2008; **24:** 995–1009.
7. Goldberg RB, *et al.* Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med* 2008; **168:** 1531–40.
8. Fonseca VA, *et al.* Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 2008; **31:** 1479–84.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Cholestagel; ***Neth.:*** Cholestagel; ***Port.:*** Cholestagel; ***UK:*** Cholestagel; ***USA:*** Welchol.

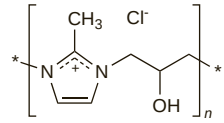
Colestilan *(rINN)*

Colestilan Chloride *(USAN)*; Colestilanum; Colestimide; MCI-196. 2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane.

Колестилан

$(C_4H_6N_2.C_3H_5ClO)_n$.

CAS — 95522-45-5.



Profile
Colestilan, a bile-acid binding resin, is a lipid regulating drug with similar properties to colestyramine (p.1252). It is used to reduce cholesterol in the management of hyperlipidaemias (p.1169) and is given orally in a usual dose of 1.5 g twice daily. It is also under investigation in diabetes mellitus and as a phosphate binder in haemodialysis patients.

◊ References.

1. Kurihara S, *et al.* Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. *Nephrol Dial Transplant* 2005; **20:** 424–30.
2. Yamakawa T, *et al.* Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. *Endocr J* 2007; **54:** 53–8.

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

Colestipol Hydrochloride

(BANM, USAN, rINNM)

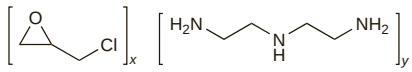
Colestipol, chlorhydrate de; Colestipoli hydrochloridum; Hidrocloruro de colestipol; Kolestipol Hidroklorür; U-26597A.

Колестипола Гидрохлорид

CAS — 26658-42-4 (colestipol); 50925-79-6 (colestipol); 37296-80-3 (colestipol hydrochloride).

ATC — C10AC02.

ATC Vet — QC10AC02.



(colestipol)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Colestipol Hydrochloride). A copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.7 mEq of sodium cholate, calculated as the cholate binding capacity and with reference to the dried substance. Yellow to orange hygroscopic beads. Swells but does not dissolve in water and in dilute solutions of acids or alkalis. Practically insoluble in alcohol and in dichloromethane. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

USP 31 (Colestipol Hydrochloride). A basic anion-exchange resin. It is the hydrochloride of a copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.6 mEq of sodium cholate, calculated as cholate binding capacity. Yellow to orange beads. Swells but does not dissolve in water or dilute aqueous solutions of acids or alkalis. Insoluble in common organic solvents. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

Adverse Effects and Precautions
As for Colestyramine, p.1252.

Effects on thyroid function. Reductions in total serum-thyroxine and thyroxine-binding globulin concentrations were found during routine monitoring of thyroid function in patients receiving colestipol and nicotinic acid, but were considered to be benign.[1] This effect has been used therapeutically in patients with hyperthyroidism (see under Uses of Colestyramine, p.1253).

1. Cashin-Hemphill L, *et al.* Alterations in serum thyroid hormonal indices with colestipol-niacin therapy. *Ann Intern Med* 1987; **107:** 324–9.

Interactions
As for Colestyramine, p.1253.

Uses and Administration
Colestipol hydrochloride is a bile-acid binding resin and lipid regulating drug with actions similar to those of colestyramine (p.1253). It is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly type IIa hyperlipoproteinaemia.

Colestipol hydrochloride is available as granules and is given orally as a suspension in water or a flavoured vehicle. The initial dose is 5 g daily or twice daily, increasing gradually at intervals of 1 to 2 months to up to 30 g daily in a single dose or two divided doses as necessary.

Colestipol hydrochloride is also available as tablets; doses range from 2 to 16 g daily.

Preparations
BP 2008: Colestipol Granules;
USP 31: Colestipol Hydrochloride for Oral Suspension; Colestipol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Colestid; ***Belg.:*** Colestid; ***Canad.:*** Colestid; ***Cz.:*** Colestid†; ***Denm.:*** Lestid; ***Fin.:*** Lestid; ***Ger.:*** Cholestabyl; Colestid; ***Gr.:*** Lestid†; ***Irl.:*** Colestid†; ***Israel:*** Colestid; ***Mex.:*** Colestid†; ***Neth.:*** Colestid†; ***Norw.:*** Lestid; ***NZ:*** Colestid; ***Port.:*** Colestid; ***Spain:*** Colestid; ***Swed.:*** Lestid; ***Switz.:*** Colestid; ***UK:*** Colestid; ***USA:*** Colestid.

Colestyramine *(BAN, rINN)*

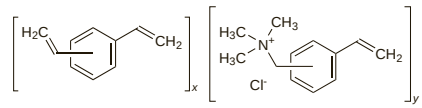
Cholestyramine; Cholestyramine Resin; Colestiramina; Colestyraminum; Divistyramine; Kolestiramin; Kolestiraminas; Kolestyramiini; Kolestyramin; Kolestyramina; MK-135.

Колестирамин

CAS — 11041-12-6.

ATC — C10AC01.

ATC Vet — QC10AC01.



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

Ph. Eur. 6.2 (Colestyramine). A strongly basic anion-exchange resin in the chloride form, consisting of styrene-divinylbenzene copolymer with quaternary ammonium groups. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated with reference to the dried material. A white or almost white, fine, hygroscopic powder. Insoluble in water, in alcohol, and in dichloromethane. A 1% suspension in water has a pH of 4.0 to 6.0 after standing for 10 minutes. Store in airtight containers.

USP 31 (Cholestyramine Resin). A strongly basic anion-exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated on the dried basis. It is used in the chloride form. A white to buff-coloured, hygroscopic, fine powder, odourless or has not more than a slight amine-like odour. It loses not more than 12% of its weight on drying. Insoluble in water, in alcohol, in chloroform, and in ether. A 1% slurry in water has a pH of 4.0 to 6.0. Store in airtight containers.

Adverse Effects
The most common adverse effect of colestyramine is constipation; faecal impaction may develop and haemorrhoids may be aggravated. Other gastrointestinal adverse effects include abdominal discomfort or pain, heartburn, flatulence, nausea, vomiting, and diarrhoea.

Colestyramine in high doses may cause steatorrhoea by interfering with the absorption of fats from the gastrointestinal tract and therefore decreased absorption of fat-soluble vitamins, such as vitamins A, D, E, and K, may occur. Chronic use of colestyramine may thus result in an increased bleeding tendency due to hypoprothrombinaemia associated with vitamin K deficiency; it also has a potential to cause osteoporosis due to impaired calcium and vitamin D absorption.

Colestyramine is the chloride form of an anion-exchange resin and prolonged use may produce hyperchloraemic acidosis, particularly in children.

Skin rashes and pruritus of the tongue, skin, and perianal region have occasionally occurred.

◊ Reviews.

1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 47C–55C.

Incidence of adverse effects. Results of the Lipid Research Clinics Coronary Primary Prevention Trial[1] involving 3806 men given colestyramine or placebo for an average of 7.4 years showed that gastrointestinal adverse effects occurred frequently in both groups but especially in the colestyramine group. In the first year 68% of the colestyramine group had at least 1 gastrointestinal adverse effect compared with 43% of the placebo group; by the seventh year the incidence had fallen to 29% and 26% respectively. Constipation and heartburn, especially, were more frequent in the colestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. These adverse effects were usually not severe and could be dealt with by standard clinical means.

The incidence of malignant neoplasms was similar in the 2 groups although there were differences in incidence at some sites. In particular, there were 21 cases of malignancy in the gastrointestinal tract (8 fatal) in the colestyramine group compared with 11 cases (1 fatal) in the placebo group. Rare cancers of the buccal cavity or pharynx were more common with colestyramine; during the study[1] there were 6 cases in the colestyramine group and none in the placebo group, and after follow-up[2] for a further 6 years and reassessment of the original diagnoses the incidences were 8 and 2, respectively. However, there was no clear dose relationship, and cigarette smoking may have been a confounder.[2] Colorectal malignancies were similar in the 2 groups, although at follow-up more non-malignant colorectal neoplasms had occurred in the colestyramine group.[2]

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA* 1984; **251:** 351–64.
2. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: results of 6 years of post-trial follow-up. *Arch Intern Med* 1992; **152:** 1399–1410.

Precautions

Colestyramine powder should be given as a suspension in water or a flavoured vehicle to minimise the risk of oesophageal obstruction.

Colestyramine should not be used in patients with complete biliary obstruction as it is unlikely to be effective.

Because of the risk of vitamin deficiencies, supplements of vitamins A, D, E, and K should be considered during prolonged therapy with colestyramine; if given orally they need to be in a water-miscible form. Parenteral supplementation, particularly of vitamin K for hypoprothrombinaemia, may be necessary if a deficiency becomes established. Reduced serum-folate concentrations have also been reported in children with familial hypercholesterolaemia and supplementation with folic acid should be considered in such circumstances.

Interactions

Colestyramine may delay or reduce the absorption of other drugs, particularly acidic drugs. Enterohepatic circulation may be reduced. Delayed or reduced absorption of thiazide diuretics, propranolol, digoxin and related glycosides, loperamide, phenylbutazone, barbiturates, oestrogens, progestogens, thyroid hormones, warfarin, and some antibacterials, has either been reported or may be expected. It is therefore recommended that other drugs should be taken at least 1 hour before, or 4 to 6 hours after, the use of colestyramine.

Uses and Administration

Colestyramine is a bile-acid binding resin and lipid regulating drug. It is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly type IIa hyperlipoproteinaemia, and for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164) in middle-aged men with primary hypercholesterolaemia. Colestyramine is also used for the relief of diarrhoea associated with ileal resection, Crohn's disease, vagotomy, diabetic vagal neuropathy, and radiation, and to relieve the pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction or primary biliary cirrhosis.

Colestyramine is not absorbed from the gastrointestinal tract and binds with bile acids in the intestine to form an insoluble complex that is excreted in the faeces. The normal reabsorption of bile acids is thus prevented and this leads to an increased oxidation of cholesterol to bile acids to replace those partially removed from the enterohepatic circulation, and an increased synthesis of low-density lipoprotein (LDL)-cholesterol receptors on hepatocytes. The overall effect is a reduction of total plasma-cholesterol concentration, mainly by lowering LDL-cholesterol; this may be accompanied by moderate increases in plasma triglyceride and high-density lipoprotein (HDL)-cholesterol concentrations. Since the uses of colestyramine are based upon the removal of intestinal bile acids it is unlikely that a response will be achieved in patients with complete biliary obstruction.

Colestyramine may be introduced gradually over 3 to 4 weeks to minimise gastrointestinal effects.

In hyperlipidaemias and diarrhoea the usual oral dose is 12 to 24 g daily, given either as a single dose or in up to 4 divided doses. Dosage should be adjusted according to the patient's response and may be increased to 36 g daily if necessary. Lower doses may be adequate in some forms of hyperlipidaemia.

In pruritus doses of 4 to 8 g daily are usually sufficient.

For the use of colestyramine in children, see below.

Colestyramine should be given as a suspension in water or a flavoured vehicle.

◊ General references.

1. Insull W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J* 2006; **99:** 257–73.

Administration in children. Colestyramine has been used in children and small studies[1,2] have found that it is effective in familial hypercholesterolaemia with no adverse effects on physical growth when taken long-term;[2] however, compliance may be a problem.[1]

For *hypercholesterolaemia*, the *BNFC* gives the usual oral dose for children aged 6 to 12 years as 4 g once daily, increased to 4 g up to 3 times daily according to response. Children aged 12 to 18 years may be given an initial dose of 4 g once daily, increased to 4 to 8 g up to 4 times daily, with a maximum daily dose of 36 g. Alternatively, licensed doses are calculated from body weight, either as a percentage of the adult (70 kg) dose, or as a dose of 240 mg/kg daily in divided doses.

For *pruritus* or *diarrhoea*, the *BNFC* recommends the following oral doses based on age:

- 1 month to 1 year: initially 1 g once daily, adjusted according to response to a maximum dose of 9 g daily in 2 to 4 divided doses
- 1 to 6 years: initially 2 g once daily, adjusted according to response to a maximum dose of 18 g daily in 2 to 4 divided doses
- 6 to 12 years: initially 4 g once daily, adjusted according to response to a maximum dose of 24 g daily in 2 to 4 divided doses
- 12 to 18 years: initially 4 to 8 g once daily, adjusted according to response to a maximum dose of 36 g daily in 2 to 4 divided doses

1. West RJ, Lloyd JK. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet* 1980; **ii:** 873–5.
2. Tonstad S, *et al.* Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996; **129:** 42–9.

Antibiotic-associated colitis. Colestyramine binds *Clostridium difficile* toxins and there are a few reports of use as an alternative, or as an adjunct, to vancomycin or metronidazole in patients with diarrhoea associated with *C. difficile* toxins after antibiotic therapy (p.171). However, evidence of benefit is limited and in general its use is not recommended.

Biliary disorders. Colestyramine is used to relieve diarrhoea (p.1694) associated with bile acid malabsorption and to manage pruritus and hypercholesterolaemia in patients with primary biliary cirrhosis (p.2408). It has been used for pruritus in cholestasis of pregnancy,[1] although such use has been associated with severe fetal intracranial haemorrhage.[2] Beneficial responses have been reported with colestyramine in the management of congenital nonobstructive nonhaemolytic hyperbilirubinaemia (Crigler-Najjar disease)[3,4] and in sclerosing cholangitis.[5]

1. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002; **36:** 1462–5.
2. Sadler LC, *et al.* Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1995; **102:** 169–70.
3. Arrowsmith WA, *et al.* Comparison of treatments for congenital nonobstructive nonhaemolytic hyperbilirubinaemia. *Arch Dis Child* 1975; **50:** 197–201.
4. Odièvre M, *et al.* Case of congenital nonobstructive, nonhaemolytic jaundice: successful long-term phototherapy at home. *Arch Dis Child* 1978; **53:** 81–2.
5. Polter DE, *et al.* Beneficial effect of cholestyramine in sclerosing cholangitis. *Gastroenterology* 1980; **79:** 326–33.

Diabetes mellitus. Bile acids may have a role in modulating carbohydrate metabolism and small studies have shown that bile-acid binding resins such as colestyramine reduce blood glucose.[1] Their role in type 2 diabetes mellitus (p.431) is under investigation; colesevelam (p.1252) may be used as an adjunct to standard therapy to improve glycaemic control.

1. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; **67:** 1383–92.

Diarrhoea. In addition to its use in diarrhoea (p.1694) associated with biliary disorders (above), colestyramine has been investigated in the management of diarrhoea and faecal incontinence from other causes.[1-4] See also Antibiotic-associated Colitis, above.

1. Baert D, *et al.* Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. *Acta Clin Belg* 2004; **59:** 258–62.
2. Balagani R, *et al.* Cholestyramine improves tropical-related diarrhea. *Am J Ther* 2006; **13:** 281–2.
3. Flieger D, *et al.* Phase II clinical trial for prevention of delayed diarrhea with cholestyramine/levofloxacin in the second-line treatment with irinotecan biweekly in patients with metastatic colorectal carcinoma. *Oncology* 2007; **72:** 10–16.
4. Remes-Troche JM, *et al.* Cholestyramine—a useful adjunct for the treatment of patients with fecal incontinence. *Int J Colorectal Dis* 2008; **23:** 189–94.

Hyperthyroidism. Bile-acid binding resins also bind thyroid hormones and may interfere with their enterohepatic circulation. Reduced serum-thyroxine concentrations have occurred in patients given bile-acid binding resins for hyperlipidaemias (see Effects on Thyroid Function under Colestipol, p.1252) and both colestyramine[1,2] and colestipol[3] have been tried as adjunctive treatment for hyperthyroidism (p.2165). Colestyramine has also been used in thyroxine overdose.[4,5]

1. Mercado M, *et al.* Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. *J Clin Endocrinol Metab* 1996; **81:** 3191–3.
2. Tsai W-C, *et al.* The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol (Oxf)* 2005; **62:** 521–4.
3. Hagag P, *et al.* Role of colestipol in the treatment of hyperthyroidism. *J Endocrinol Invest* 1998; **21:** 725–31.
4. Shakir KMM, *et al.* The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med* 1993; **118:** 112–13.
5. de Luis DA, *et al.* Light symptoms following a high-dose intentional L-thyroxine ingestion treated with cholestyramine. *Horm Res* 2002; **57:** 61–3.

Preparations

BP 2008: Colestyramine Oral Powder;
USP 31: Colestyramine for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

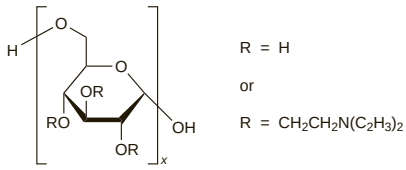
Arg.: Questran; ***Austral.:*** Questran; ***Austria:*** Quantalan; ***Belg.:*** Questran; ***Braz.:*** Questran; ***Canad.:*** Novo-Cholamine; Questran†; ***Cz.:*** Questran; Vasosan†; ***Denm.:*** Questran; ***Fin.:*** Questran; ***Fr.:*** Questran; ***Ger.:*** Colesthexal†; Colestyr; Lipocol; Quantalan; Vasosan; ***Gr.:*** Questran; ***Hong Kong:*** Questran; ***Indon.:*** Questran; ***Irl.:*** Questran; ***Israel:*** Chol-Less†; ***Ital.:*** Questran; ***Malaysia:*** Questran†; ***Mex.:*** Questran; ***Neth.:*** Questran; ***Norw.:*** Questran; ***NZ:*** Questran; ***Pol.:*** Vasosan; ***Port.:*** Quantalan; ***S.Afr.:*** Questran; ***Singapore:*** Questran; Resincolestiramina†; ***Spain:*** Efensol; Lismol†; Questran†; Resincolestiramina; ***Swed.:*** Questran; ***Switz.:*** Ipocol; Quantalan; ***Thai.:*** Questran; Resincolestiramina; ***Turk.:*** Kolestran; ***UK:*** Questran; ***USA:*** Locholest; Prevalite; Questran.

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.

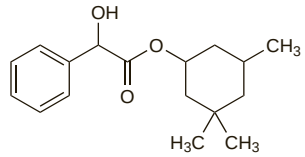
Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Pulsar; Rationale; ***Spain:*** Dexide.

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.

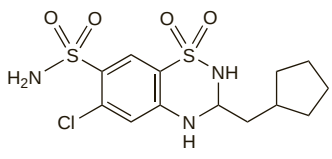
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Cyclospasmol†; ***Fin.:*** Cyclospasmol†; ***Fr.:*** Cyclergine†; Vascunormyl†; ***Ger.:*** Natil; Spasmocyclon†; ***India:*** Martispasmol†; ***Ital.:*** Ciclospasmol†; ***Neth.:*** Cyclospasmol; ***Port.:*** Cyclospasmol†; ***Swed.:***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

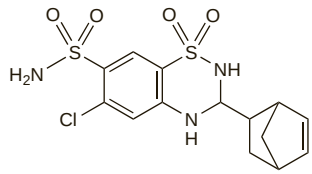
Multi-ingredient: ***Hong Kong:*** Navispare; ***S.Afr.:*** Lenurex-K; ***UK:*** Navispare; Trasidrex.

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.



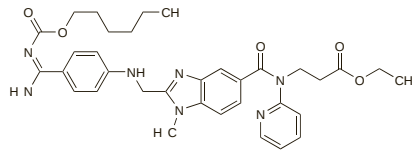
Profile
Cyclothiazide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used, usually in combination preparations, in the management of hypertension and oedema.

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.