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.

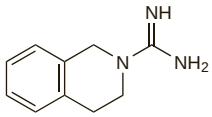
Дебризохина Сульфат

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

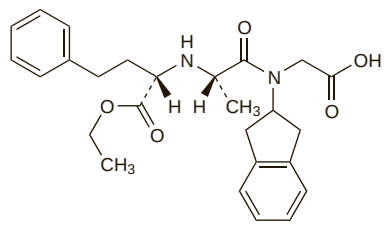
Делаприла Гидрохлорид

$C_{26}H_{32}N_2O_5$,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.

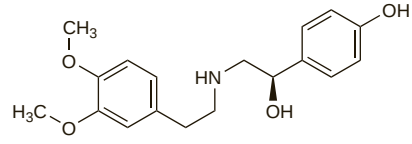
Denopamine *(rINN)*

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.

Deserpidine *(BAN, rINN)*

Canescine; Deserpidiini; Deserpidin; Deserpidina; Déserpidine; Deserpidinum; 11-Desmethoxyreserpine; Raunormine; Recanescine. Methyl 11-demethoxy-*O*-(3,4,5-trimethoxybenzoyl)reserpate.

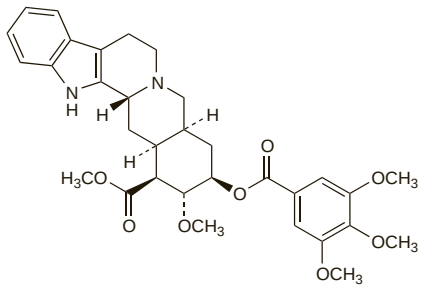
Дезерпидин

$C_{32}H_{38}N_2O_8$ = 578.7.

CAS — 131-01-1.

ATC — C02AA05.

ATC Vet — QC02AA05.



Profile

Deserpidine is an ester alkaloid isolated from the root of *Rauwolfia canescens*. It has properties similar to those described under reserpine (p.1387) and has been used in the treatment of hypertension and psychoses.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Hong Kong:*** Enduronyl†.

Desirudin *(BAN, USAN, rINN)*

CGP-39393; Desirudiini; Desirudina; Désirudine; Desirudinum; Desulphatohirudin. 63-Desulfohirudin (*Hirudo medicinalis* isoform HV1).

Дезирудин

$C_{287}H_{440}N_{80}O_{110}S_6$ = 6963.4.

CAS — 120993-53-5.

ATC — B01AE01.

ATC Vet — QB01AE01.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

Teratogenicity has been observed in *animals*.

Interactions

As for Lepirudin, p.1323.

Pharmacokinetics

Maximum plasma concentrations of desirudin are reached 1 to 3 hours after subcutaneous injection. Desirudin is metabolised and excreted by the kidney, and 40 to 50% of a dose is excreted unchanged in the urine. After subcutaneous or intravenous injection the terminal elimination half-life of desirudin is 2 to 3 hours.

◊ References.

1. Lefèvre G, *et al.* Effect of renal impairment on the pharmacokinetics and pharmacodynamics of desirudin. *Clin Pharmacol Ther* 1997; **62:** 50–9.

Uses and Administration

Desirudin is a recombinant hirudin (p.1305) that is a direct inhibitor of thrombin with actions similar to Lepirudin, p.1323. It is used as an anticoagulant for the prevention of postoperative venous thromboembolism (p.1189) in patients undergoing orthopaedic surgery. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina, and as an adjunct in angioplasty procedures (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p.1323).

In the prevention of venous thromboembolism, desirudin is given subcutaneously in a dose of 15 mg twice daily, the first dose 5 to 15 minutes before surgery, but after induction of regional block anaesthesia, if used. Treatment is continued until the patient is fully ambulant, usually for 9 to a maximum of 12 days.

Response to desirudin should be monitored using activated partial thromboplastin time (APTT) in patients with hepatic or renal impairment, or increased risk of bleeding. Doses may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Matheson AJ, Goa KL. Desirudin: a review of its use in the management of thrombotic disorders. *Drugs* 2000; **60:** 679–700.

Administration in renal impairment. The dose of desirudin should be reduced in patients with renal impairment, depending on creatinine clearance (CC) and activated partial thromboplastin time (APPT), which should be measured daily. US licensed product information recommends the following doses:

- CC 31 to 60 mL/minute per 1.73 m^2, initial dose 5 mg every 12 hours, subsequently adjusted according to APPT
- CC below 31 mL/minute per 1.73 m^2, initial dose 1.7 mg every 12 hours, subsequently adjusted according to APPT

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Revasc; ***Cz.:*** Revasc; ***Fr.:*** Revasc†; ***Ger.:*** Revasc; ***Gr.:*** Revasc†; ***Hung.:*** Revasc†; ***Neth.:*** Revasc; ***Norw.:*** Revasc†; ***NZ:*** Revasc; ***Port.:*** Revasc; ***Spain:*** Revasc; ***Switz.:*** Revasc†; ***USA:*** Iprivask.

Deslanoside *(BAN, rINN)*

Deacetyl-lanatoside C; Desacetyl-lanatoside C; Deslanosid; Deslanosídeo; Deslanosidi; Deslanósido; Deslanosidum; Deslanozidas; Dezlanozid. 3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)-oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

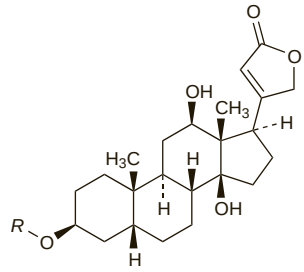
Дезланозид

$C_{47}H_{74}O_{19}$ = 943.1.

CAS — 17598-65-1.

ATC — C01AA07.

ATC Vet — QC01AA07.



R = β-D-glucose–(β-D-digitoxose)$_3$

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Deslanoside). A white or almost white, crystalline or finely crystalline hygroscopic powder. Practically insoluble in water; very slightly soluble in alcohol. In an atmosphere of low relative humidity, it loses water. Store in airtight, glass containers at a temperature below 10°. Protect from light.
USP 31 (Deslanoside). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Deslanoside, a cardiac glycoside with positive inotropic activity, is a derivative of lanatoside C. It has the general properties of digoxin (p.1259) and has been used similarly in the management of some cardiac arrhythmias and in heart failure.

Preparations

USP 31: Deslanoside Injection.

Proprietary Preparations (details are given in Part 3)
Braz.: Cedilanide.

Detajmium Bitartrate *(rINN)*

Bitartrato de detajmio; Detajmii Bitartras; Détajmium, Bitartrate de. 4-[3-(Diethylamino)-2-hydroxypropyl]ajmalinium hydrogen tartrate monohydrate.

Детаймия Битартрат

$C_{31}H_{47}N_3O_9,H_2O$ = 623.7.

CAS — 53862-81-0.

Profile

Detajmium is a class I antiarrhythmic (p.1153). It is given orally as the bitartrate, in the treatment of supraventricular and ventricular arrhythmias (p.1160). The dose range is from 75 to 300 mg daily depending upon the arrhythmia.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Tachmalcor; ***Ger.:*** Tachmalcor.

Diazoxide *(BAN, USAN, rINN)*

Diatsoksidi; Diazoksidas; Diazoksit; Diazoxid; Diazóxido; Diazoxidum; NSC-64198; Sch-6783; SRG-95213. 7-Chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide.

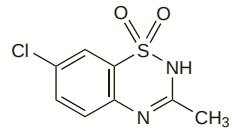
Диазоксид

$C_8H_7ClN_2O_2S$ = 230.7.

CAS — 364-98-7.

ATC — C02DA01; V03AH01.

ATC Vet — QC02DA01; QV03AH01.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*.
Ph. Eur. 6.2 (Diazoxide). A white or almost white, fine or crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide; very soluble in dilute solutions of alkali hydroxides.
USP 31 (Diazoxide). White or cream-white crystals or crystalline powder. Practically insoluble to sparingly soluble in water and in most organic solvents; freely soluble in dimethylformamide; very soluble in strong alkaline solutions. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

In addition to inappropriate hypotension and hyperglycaemia (which includes ketoacidosis and hyperosmolar nonketotic coma), adverse effects often include oedema due to salt and water retention, which may precipitate heart failure. Other adverse effects include: dysgeusia, nausea, anorexia, and other gastrointestinal disturbances; mild hyperuricaemia; extrapyramidal symptoms; eosinophilia and thrombocytopenia; dyspnoea; hypertrichosis; and headache, dizziness, tinnitus, and blurred vision. Hypersensitivity has occurred, manifesting as rashes, leucopenia, and fever.

During intravenous therapy, particularly after large bolus injections, adverse effects may be associated with too rapid a reduction in blood pressure and include: coronary ischaemia leading to angina, cardiac arrhythmias, marked ECG changes, tachycardia, palpitations, and bradycardia; cerebral ischaemia leading to confusion, convulsions, loss of consciousness, and neurological deficit; renal impairment; and symptoms of vasodilatation.

Diazoxide may cause a burning sensation in the injected vein; extravasation of the alkaline solution is painful.

Effects on the blood. A 26-year-old man with hypertension developed reversible haemolytic anaemia when treated with diazoxide orally on 3 separate occasions.[1]

1. Best RA, Clink HM. Haemolysis associated with diazoxide, used for the control of hypertension. *Postgrad Med J* 1975; **51:** 402–4.

Effects on the hair. *Hirsutism* and *hypertrichosis* are different types of excessive hair growth, but the terms have often been used interchangeably. Hirsutism is androgen-related whereas hypertrichosis is thought to be independent of hormone stimulation. Hypertrichosis is acknowledged to be a frequent adverse effect of diazoxide in children receiving long-term treatment for idiopathic hypoglycaemia.[1] Two such children had unusually deep (low-pitched) voices as well as marked hypertrichosis.[2] A woman on continuous diazoxide therapy who developed so-called hirsutism without signs of virilisation had raised serum concentrations of androgens.[3]

Alopecia has been reported[4] in 4 infants born to mothers who had been on long-term treatment with diazoxide during pregnancy; the condition was still present to some extent when the infants were last observed at the ages of 5 months to 1 year.

1. Burton JL, *et al.* Hypertrichosis due to diazoxide. *Br J Dermatol* 1975; **93:** 707–11.
2. West RJ. Side effects of diazoxide. *BMJ* 1978; **2:** 506.
3. Hallengren B, Hökfelt B. Increase of serum androgens during diazoxide treatment. *Lancet* 1984; **ii:** 1044–5.
4. Milner RDG, Chouksey SK. Effects of fetal exposure to diazoxide in man. *Arch Dis Child* 1972; **47:** 537–43.