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.

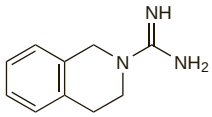
Дебризохина Сульфат

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

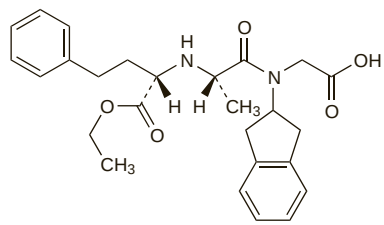
Делаприла Гидрохлорид

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

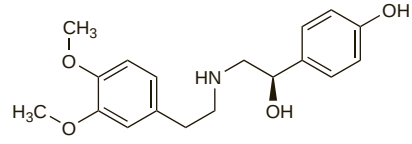
Denopamine *(rINN)*

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.