### Deserpidine *(BAN, rINN)*

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

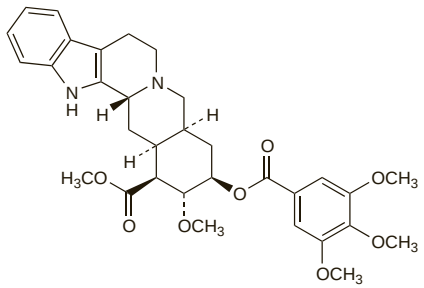
Дезерпидин

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

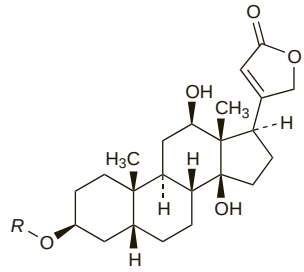
Дезланозид

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

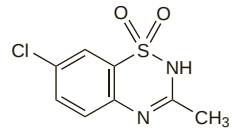
Диазоксид

$C_8H_7ClN_2O_2S$ = 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.

**Extrapyramidal effects.** In a study[1] of 100 hypertensive patients receiving diazoxide, the incidence of extrapyramidal symptoms was 15%.

1. Pohl JEF. Development and management of extrapyramidal symptoms in hypertensive patients treated with diazoxide. *Am Heart J* 1975; **89:** 401–2.

**Pancreatitis.** Ten patients with severe hypertension and renal failure were treated with diazoxide in a last attempt to avert nephrectomy; 1 patient developed acute pancreatitis and another diabetic ketoacidosis.[1] Both patients recovered from these effects when diazoxide was withdrawn.

1. De Broe M, *et al*. Oral diazoxide for malignant hypertension. *Lancet* 1972; **i:** 1397.

**Voice changes.** See Effects on the Hair, above.

## Treatment of Adverse Effects

Treatment is largely symptomatic. Severe hyperglycaemia may be corrected by giving insulin: less severe hyperglycaemia may respond to oral hypoglycaemics. Hypotension may be managed with intravenous fluids. Severe hypotension may require sympathomimetics. Antiparkinsonian drugs, such as procyclidine, have been given to control extrapyramidal effects while a diuretic may be required for salt and water retention. Diazoxide can be removed from the body by dialysis but recovery is relatively low owing to extensive protein binding.

## Precautions

Diazoxide should be used with care in patients with impaired cardiac or cerebral circulation and in patients with aortic coarctation, arteriovenous shunt, heart failure, or other cardiac disorders in which an increase in cardiac output could be detrimental. During prolonged therapy blood-glucose concentrations and blood pressure should be monitored and the blood should be examined regularly for signs of leucopenia and thrombocytopenia; in children, bone and psychological maturation, and growth, should be regularly assessed. Caution is necessary in patients with renal impairment.

If given during labour, diazoxide may cause cessation of uterine contractions and delay delivery unless oxytocin is also given.

**Pregnancy.** Transplacental transfer of diazoxide was considered[1] to be responsible for an inappropriately low plasma-insulin concentration in an infant whose mother had received a dose of 150 mg daily for 47 days prior to delivery. For reference to alopecia in neonates whose mothers had received diazoxide during pregnancy, see Effects on the Hair under Adverse Effects, above.

For reports of sedation, hypotonia, or apnoea among infants born to mothers given both diazoxide and clomethiazole for the treatment of toxaemia of pregnancy, see Precautions, Pregnancy, in Clomethiazole Edisilate, p.978. Diazoxide is nonetheless one of the drugs that has been used for hypertensive emergencies in pregnancy (see Hypertension, p.1171) and a study found that mini-boluses of diazoxide 15 mg intravenously successfully reduced blood pressure and were well tolerated.[2]

1. Smith MJ, *et al*. Neonatal hyperglycaemia after prolonged maternal treatment with diazoxide. *BMJ* 1982; **284:** 1234.
2. Hennessy A, *et al*. A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007; **47:** 279–85.

## Interactions

The hyperglycaemic, hyperuricaemic, and hypotensive actions of diazoxide may be enhanced by diuretics. Use of diazoxide with other antihypertensives or vasodilators may lead to increased risk of hypotension.

**Chlorpromazine.** Chlorpromazine was reported[1] to enhance the hyperglycaemic effect of diazoxide in a 2-year-old child.

1. Aynsley-Green A, Illig R. Enhancement by chlorpromazine of hyperglycaemic action of diazoxide. *Lancet* 1975; **ii:** 658–9.

**Phenytoin.** For the effect of diazoxide on serum-phenytoin concentrations, see Antihypertensives, p.499.

## Pharmacokinetics

Diazoxide is readily absorbed from the gastrointestinal tract and more than 90% bound to plasma proteins, although protein binding is decreased in uraemic patients. Its plasma half-life has been estimated to range from about 20 to 45 hours but values of up to 60 hours have been reported. The half-life is reported to be prolonged in renal impairment and shorter for children. The plasma half-life greatly exceeds the duration of vascular activity. Diazoxide is partly metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites; only small amounts are recovered from the faeces. It crosses the placenta and the blood-brain barrier.

**Children.** In 4 children with hypoglycaemia the plasma half-life of diazoxide was 9.5 to 24 hours, which is considerably shorter than that in adults.[1]

1. Pruitt AW, *et al*. Disposition of diazoxide in children. *Clin Pharmacol Ther* 1973; **14:** 73–82.

## Uses and Administration

Diazoxide increases the concentration of glucose in the plasma; it inhibits the secretion of insulin by the beta cells of the pancreas, and may increase the hepatic output of glucose. When given intravenously, it produces a fall in blood pressure by a vasodilator effect on the arterioles and a reduction in peripheral resistance. Diazoxide is closely related structurally to the thiazide diuretics, but has an antidiuretic action and thus produces fluid and electrolyte retention; it may be given with a diuretic to reduce fluid retention.

Diazoxide is used orally in the management of intractable hypoglycaemia (p.1447) and intravenously in the management of hypertensive crises (p.1171), particularly when first-line drugs such as sodium nitroprusside are ineffective or unsuitable. Diazoxide is not suitable for the chronic treatment of hypertension because of its severe adverse effects.

In **hypoglycaemia**, the initial dose is 3 to 5 mg/kg daily in 2 or 3 divided oral doses, then adjusted according to response. Usual maintenance doses are from 3 to 8 mg/kg daily but total doses of up to 1 g daily have been given to adults with insulinomas (see Carcinoid Tumours and other Secretory Neoplasms, p.643). In neonates the initial dose is 5 mg/kg twice daily; usual maintenance doses range from 3 to 9 mg/kg daily, although up to 21 mg/kg daily may be required. In children from 1 month of age, the initial dose is 1.7 mg/kg three times daily, and the usual maintenance doses are as for neonates; up to 15 mg/kg daily may be required. The hyperglycaemic effect normally begins within 1 hour of a dose and lasts for up to 8 hours. The doses for neonates and children may be given intravenously if necessary.

In **hypertensive crises**, a bolus intravenous injection of 1 to 3 mg/kg is given within 30 seconds, up to a maximum dose of 150 mg, and repeated after 5 to 15 minutes if required.

Reduced doses may be necessary in patients with renal impairment.

## Preparations

***BP 2008:*** Diazoxide Injection; Diazoxide Tablets;
***USP 31:*** Diazoxide Capsules; Diazoxide Injection; Diazoxide Oral Suspension.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Proglicem; ***Braz.:*** Tensuril; ***Canad.:*** Hyperstat†; Proglycem; ***Fr.:*** Proglicem; ***Ger.:*** Hypertonalum†; Proglicem; ***Gr.:*** Eudemine; Hyperstat†; Proglycem; ***Ital.:*** Hyperstat†; Proglicem; ***Mex.:*** Hyperstat†; Sefulken; ***Neth.:*** Proglicem; ***Swed.:*** Hyperstat†; ***Switz.:*** Proglicem; ***UK:*** Eudemine; ***USA:*** Hyperstat; Proglycem.

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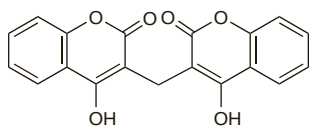
## Dicoumarol *(rINN)*

Bishydroxycoumarin; Dicoumarin; Dicoumarolum; Dicumarol *(USAN)*; Dikumarol; Dikumaroli; Melitoxin. 3,3′-Methylenebis(4-hydroxycoumarin).

Дикумарол

$C_{19}H_{12}O_6$ = 336.3.
*CAS — 66-76-2.*
*ATC — B01AA01.*
*ATC Vet — QB01AA01.*



**Pharmacopoeias.** In *Int.*

## Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425, although gastrointestinal adverse effects are reported to occur more frequently. The absorption of dicoumarol is affected by food.

**Breast feeding.** No adverse effects have been seen in breastfeeding infants whose mothers were receiving dicoumarol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

## Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving dicoumarol can be found under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antidiabetics; antiepileptics; antigout drugs; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; sex hormones; and vitamins.

## Pharmacokinetics

Dicoumarol is slowly and erratically absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites.

## Uses and Administration

Dicoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It has been used in the management of thromboembolic disorders (p.1187). The usual daily maintenance dose, adjusted according to coagulation tests, is 25 to 200 mg.

Because of its unpredictability of response and high incidence of gastrointestinal effects, dicoumarol has been largely replaced by warfarin.

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## Digitalis Leaf

Digit. Fol.; Digit. Leaf; Digital, hoja de; Digitale Pourprée; Digitale Pourprée, Feuille de; Digitaliksenlehti; Digitalis; Digitalis Folium; Digitalis purpureae folium; Digitalisblad; Feuille de Digitale; Fingerhutblatt; Folha de Dedaleira; Foxglove Leaf; Hoja de Digital; List náprstníku červeného; Piros gyűszűvirághlevél; Rusmenių lapai.

*ATC — C01AA03.*
*ATC Vet — QC01AA03.*

NOTE. The term 'digitalis' is often used to describe the entire class of cardiac glycosides.

**Pharmacopoeias.** In *Eur.* (see p.vii) and *US.*
**Ph. Eur. 6.2** (Digitalis Leaf). The dried leaf of *Digitalis purpurea*. It contains not less than 0.3% of cardenolic glycosides, expressed as digitoxin, and calculated with reference to the drug dried at 100° to 105°. Protect from light and moisture.
**USP 31** (Digitalis). The dried leaf of *Digitalis purpurea* (Scrophulariaceae). The potency is such that, when assayed as directed, 100 mg is equivalent to not less than 1 USP unit. Store in containers that protect it from absorbing moisture.

## Profile

Digitalis leaf contains a number of cardiac glycosides with positive inotropic activity, including digitoxin, gitoxin, and gitaloxin. It has the general properties described under digoxin (p.1259) and has been used similarly in the management of heart failure. However, when treatment with a cardiac glycoside is required a single glycoside is preferred to digitalis, and digoxin or digitoxin are most commonly used.

Digitalis is used in herbal medicine.

**Homoeopathy.** Digitalis leaf has been used in homoeopathic medicines under the following names: Digitalis; Digitalis purpurea; Dig. pur.

## Preparations

***USP 31:*** Digitalis Capsules; Digitalis Tablets.

**Proprietary Preparations** (details are given in Part 3)
***Ger.:*** Digophton†.

**Multi-ingredient:** ***Austria:*** Augentropfen Stulln; ***Ger.:*** Augentropfen Stulln Mono; Unguentum lymphaticum; ***Switz.:*** Augentonicum; Collypan; ***Venez.:*** Linfoderm.

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## Digitalis Lanata Leaf

Austrian Digitalis; Austrian Foxglove; Digitalis lanata, hoja de; Digitalis Lanatae Folium; Woolly Foxglove Leaf.

*CAS — 17575-20-1 (lanatoside A).*

## Profile

Digitalis lanata leaf consists of the dried leaves of the woolly foxglove, *Digitalis lanata* (Scrophulariaceae), containing about 1 to 1.4% of a mixture of cardioactive glycosides, including digoxin, digitoxin, acetyldigoxin, acetyldigitoxin, lanatoside A, and deslanoside.