exists as a mixture of alpha- and beta-isomers. The ratio of alpha- to beta-isomers is not less than 1.5:1.0 and not more than 2.5:1.0. A white to off-white, microcrystalline or amorphous, practically odourless powder. Slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. A 0.5% solution in water has a pH of 4.2 to 5.2. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects occasionally reported with codergocrine mesilate include abdominal cramps, nausea, vomiting, headache, blurred vision, skin rashes, nasal congestion, flushing of the skin, dizziness, bradycardia, and orthostatic hypotension.

Local irritation has occurred after sublingual use.

Effects on the cardiovascular system. Of 8 patients given codergocrine mesilate 1.5 mg three times daily for the treatment of dementia, 3 developed severe sinus bradycardia associated with general deterioration in their condition, necessitating withdrawal of the treatment.[1] However, no sinus bradycardia had been seen in 40 elderly patients in whom the dose was built up to 1.5 mg three times daily over 3 weeks.[2]

1. Cayley ACD, *et al.* Sinus bradycardia following treatment with Hydergine for cerebrovascular insufficiency. *BMJ* 1975; **4:** 384–5.
2. Cohen C. Sinus bradycardia following treatment with Hydergine. *BMJ* 1975; **4:** 581.

Precautions

Codergocrine mesilate should be used with caution in patients with severe bradycardia.

Pharmacokinetics

Codergocrine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 1 to 2 hours after an oral dose. Oral bioavailability is low; this has been attributed to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism. It is 81% bound to plasma proteins. Elimination is biphasic with a short half-life of 1.5 to 2.5 hours (α phase) and a longer half-life of 13 to 15 hours (β phase). Codergocrine is mainly excreted with bile in the faeces, although small amounts are eliminated in the urine as metabolites and unchanged drug.

Uses and Administration

Unlike the natural ergot alkaloids, codergocrine mesilate has only limited vasoconstrictor effects.

A mixture of hydrogenated ergot alkaloids, codergocrine mesilate is used as an adjunct in the symptomatic treatment of mild to moderate dementia in the elderly (see also below). It is given in oral doses of 3 or 4.5 mg daily, preferably before meals. Higher doses have also been used. It is also given sublingually in similar doses. It has been given intramuscularly, subcutaneously, or by intravenous infusion.

In some countries, codergocrine mesilate has been used in the treatment of hypertension, migraine, and in peripheral vascular disease.

Codergocrine esilate has been used similarly to the mesilate.

Dementia. Codergocrine has been used for many years in dementia (p.362) but its value is not established.[1-3] Originally its effects were thought to be mediated through peripheral and cerebral vasodilatation but it is now classified as a metabolic enhancer.

1. Wadworth AN, Chrisp P. Co-dergocrine mesylate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in age-related cognitive decline. *Drugs Aging* 1992; **2:** 153–73.
2. Schneider LS, Olin JT. Overview of clinical trials of Hydergine in dementia. *Arch Neurol* 1994; **51:** 787–98.
3. Olin J, *et al.* Hydergine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 13/02/06).

Erectile dysfunction. For reference to the use of creams containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

Preparations

BP 2008: Codergocrine Tablets;
USP 31: Ergoloid Mesylates Capsules; Ergoloid Mesylates Oral Solution; Ergoloid Mesylates Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: CCK†; Coplexina; Ergoxina†; Hydergina; Somoblon†; Vimotadine; ***Austria:*** Dorehydrin; Ergomed; Hydergin; ***Belg.:*** Hydergine; Ibexone; Stofilan; ***Braz.:*** Hydergine; ***Canad.:*** Hydergine; ***Chile:*** Geroplus†; Hydergina†; ***Cz.:*** Secatoxin Forte; ***Fin.:*** Artergin†; Hydergin; ***Fr.:*** Capergyl; Ergodose†; Hydergine; ***Ger.:*** Circanol†; DCCK; Defluina N†; Ergodesit; ergotox; Hydergin; Hydro-Cebral; Orphol; Sponsin; ***Gr.:*** Engestol-Hyd†; Huperloid†; Hydergine; Santamin†; Zodalin†; ***Hong Kong:*** Hydergine; Perenan†; Stofilan; Trigogine; ***Hung.:*** Redergam†; ***India:*** Cereloid; ***Indon.:*** Cirloid; Ergotika; Exergin; Fontula; Hydergin; Procere; Xepadergin; ***Israel:*** Hydergine; ***Ital.:*** Hydergina; Ischelium†; ***Malaysia:*** Beagocrine†; Headgen; Hydergine; Vasculin†; ***Mex.:*** Hydergina; ***Philipp.:*** Hydergine; ***Port.:*** Hydergine; Redergot†; Secamin†; ***Singapore:*** Headgen; Hydergine; Trigogine; ***Spain:*** Ergodilat†; Hydergina; ***Swed.:*** Hydergin; ***Switz.:*** Ergohydrine; Hydergine; ***Thai.:*** Codergine†; Helcon; Hyceral; Hydergine; Hydrine; Hymed; Naline; Perenan†; Redergin†; Togine; Trigogine; Vasculin; Vasian; ***Turk.:*** Segol; ***UK:*** Hydergine†; ***USA:*** Gerimal; Hydergine; ***Venez.:*** Astergina; Hyderan†; Hydergina†.

Multi-ingredient: ***Arg.:*** CCK Flunarizina†; Difusil; Neuriclor Vascular†; Neuronal Vascular†; Reagin Vascular; ***Austria:*** Pontuc; ***Braz.:*** Vincetron†; ***Port.:*** Euvifor†; ***Spain:*** Clinadil Compositum; Piracetam Complex†.

Dihydroergocristine Mesilate *(BANM)*

Dihidroergocristina, mesilato de; Dihidroergokristino mesilatas; Dihidroergokrisztin-mezilát; Dihydroergocristine, mésilate de; Dihydroergocristine Mesylate; Dihydroergocristine Methanesulphonate; Dihydroergocristini mesilas; Dihydroergokristiinimesilaatti; Dihydroergokristinmesilat; Dihydroergokristin-mesylát.

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-isopropyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulphonate.

$C_{35}H_{41}N_5O_5,CH_4O_3S$ = 707.8.

CAS — 17479-19-5 (dihydroergocristine); 24730-10-7 (dihydroergocristine mesilate).

ATC — C04AE04.

ATC Vet — QC04AE04.

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

Ph. Eur. 6.2 (Dihydroergocristine Mesilate). A white or almost white, fine crystalline powder. Slightly soluble in water; soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

Profile

Dihydroergocristine mesilate is a component of codergocrine mesilate (above) and has similar actions. In some countries it has been given orally in doses of 3 to 6 mg daily in divided doses in the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency and in peripheral vascular disease. It has also been given by intramuscular or intravenous injection.

◊ References.

1. Franciosi A, Zavattini G. Dihydroergocristine in the treatment of elderly patients with cognitive deterioration: a double-blind, placebo-controlled, dose-response study. *Curr Ther Res* 1994; **55:** 1391–1401.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nehydrin; ***Braz.:*** Iskemil; Iskevert†; ***Gr.:*** Agiobita; Alfacrist; Beytina; Cristil; Diertina; Ergobel; Ergocrist; Ergofil; Fenitina; Guadal; Memotil; Mentidose†; Normocedon; Thriolan; Tonergon; ***Ital.:*** Defluina†; Diertina†; Difluid†; ***Port.:*** Diertina; ***Spain:*** Diertine; Ergodavur.

Multi-ingredient: ***Arg.:*** Cervilane; Cinacris; Micerfin; ***Austria:*** Brinerdin; Defluina; ***Braz.:*** Isketam; Norogil; Vertizine D; ***Chile:*** Cervilane; ***Cz.:*** Anavenol; Crystepin; Ersilan; Neocrystepin; Trimecryton†; ***Fr.:*** Iskedyl; ***Ital.:*** Brinerdina; ***Mex.:*** Cervilan; ***Pol.:*** Anavenol; Normatens; Venacorn; ***Port.:*** Brinerdine†; Cervilane†; ***Rus.:*** Anavenol (Анавенол); Crystepin (Кристепин); ***S.Afr.:*** Brinerdin; ***Spain:*** Brinerdina†; Clinadil; Diemil; ***Switz.:*** Brinerdine; ***Thai.:*** Bedin; Brinerdin; Hyperdine†.

Dihydroergocryptine Mesilate

Dihidroergocriptina, mesilato de; Dihydroergocryptine Mesylate; Dihydroergocryptine Methanesulphonate; Dihydroergokryptine Mesylate.

$C_{32}H_{43}N_5O_5,CH_4O_3S$ = 673.8.

CAS — 25447-66-9 (dihydroergocryptine, α-isomer); 19467-62-0 (dihydroergocryptine, β-isomer); 14271-05-7 (dihydroergocryptine mesilate, α-isomer); 65914-79-6 (dihydroergocryptine mesilate, β-isomer).

ATC — N04BC03.

ATC Vet — QN04BC03.

Profile

Dihydroergocryptine mesilate is a component of codergocrine mesilate (p.363) and has similar actions. It has been given orally in doses of up to 20 mg daily for migraine, and in maintenance doses of up to 60 to 120 mg daily for parkinsonism. It has also been used for age-related dementia and to inhibit lactation. In some countries it has been given with caffeine for cerebrovascular and peripheral vascular disorders.

◊ References.

1. Scarzella L, *et al.* Dihydroergocryptine in the management of senile psycho-organic syndrome. *Int J Clin Pharmacol Res* 1992; **12:** 37–46.
2. Battistin L, *et al.* Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. *Acta Neurol Scand* 1999; **99:** 36–42.
3. Bergamasco B, *et al.* Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. *Acta Neurol Scand* 2000; **101:** 372–80.
4. Micieli G, *et al.* Alpha-dihydroergocryptine and predictive factors in migraine prophylaxis. *Int J Clin Pharmacol Ther* 2001; **39:** 144–51.
5. Tergau F, *et al.* Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Mov Disord* 2001; **16:** 731–5.
6. Albanese A, Colosimo C. Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. *Acta Neurol Scand* 2003; **107:** 349–55.
7. Mailland E, *et al.* Alpha-dihydroergocryptine in the long-term therapy of Parkinson's disease. *Arzneimittelforschung* 2004; **54:** 647–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Almirid; ***Ger.:*** Almirid; Cripar; ***Gr.:*** Daverium; ***Ital.:*** Daverium; ***Mex.:*** Diamin; ***Pol.:*** Almirid; ***Port.:*** Striatal; ***Rus.:*** Vasobral (Вазобрал); ***Switz.:*** Cripar.

Multi-ingredient: ***Fr.:*** Vasobral; ***Hong Kong:*** Vasobral; ***Ital.:*** Vasobral†.

Donepezil Hydrochloride

(BANM, USAN, rINNM)

BNAG; Donépézil, Chlorhydrate de; Donepezil Hidroklorür; Donepezili Hydrochloridum; E-2020; ER-4111 (donepezil); Hidrocloruro de donepezilo. (±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride.

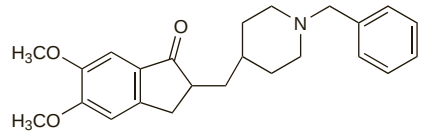
Донепезила Гидрохлорид

$C_{24}H_{29}NO_3,HCl$ = 416.0.

CAS — 120014-06-4 (donepezil); 142057-79-2 (donepezil); 120011-70-3 (donepezil hydrochloride); 142057-77-0 (donepezil hydrochloride).

ATC — N06DA02.

ATC Vet — QN06DA02.



(donepezil)

Adverse Effects and Treatment

Adverse effects of acetylcholinesterase inhibitors such as donepezil notably include nausea, vomiting, anorexia, diarrhoea, fatigue, and dizziness. Other common adverse effects include abdominal pain, dyspepsia, rash, pruritus, headache, somnolence, muscle cramps, insomnia, sweating, tremor, and syncope; upper-respiratory-tract and urinary-tract infections have been noted. Rare cases of angina, sino-atrial and AV blocks, bradycardia, peptic ulcers, gastrointestinal haemorrhage, extrapyramidal symptoms, and seizures have been observed. Psychiatric disturbances, including depression, hallucinations, agitation, aggressive behaviour, and confusion have also been reported. There is a potential for bladder outflow obstruction. Minor increases in serum-creatine kinase have also occurred with donepezil.

Hepatotoxicity has occurred with tacrine, and has limited its use (see Tacrine, Precautions, p.370); individual cases of increased liver transaminases have been noted with other acetylcholinesterase inhibitors.

The use of acetylcholinesterase inhibitors has been associated with weight loss and consequently some licensed product information has recommended that a patient's weight is monitored during treatment. Female patients have been found to be more susceptible to nausea, vomiting, anorexia, and weight loss.

Overdosage with cholinesterase inhibitors may result in 'cholinergic crisis', the details of which are described under Adverse Effects of Neostigmine, p.631.

◊ Reviews of the safety profile of donepezil.

1. Committee on Safety of Medicines/Medicines Control Agency. Donepezil (Aricept). *Current Problems* 1999; **25:** 7.
   Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 13/08/07)
2. Jackson S, *et al.* The safety and tolerability of donepezil in patients with Alzheimer's disease. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 1–8.