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.

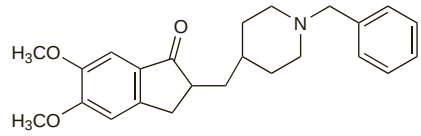
Донепезила Гидрохлорид

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

Effects on the cardiovascular system. The Australian Adverse Drug Reactions Advisory Committee noted in October 2004 that it had received 32 reports of cardiac arrhythmias associated with donepezil (14 of bradycardia, 1 bundle branch block, 5 AV blocks, 10 cases of syncope, and 2 unspecified), as well as 7 cases of myocardial infarction or cardiac arrest.[1] There had been 7 reports of similar cardiovascular effects with rivastigmine and 6 with galantamine; the larger number with donepezil was almost certainly due to wider usage of this drug. Most patients recovered when the drug was stopped or the dose reduced, though many were hospitalised and in 4 cases a pacemaker was required.

One study in vascular dementia reported an increased death rate with donepezil (see Dementia, below) but no increase in vascular events.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cholinesterase inhibitors and cardiac arrhythmias. *Aust Adverse Drug React Bull* 2004; **23:** 19–20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 13/02/06)

Effects on the nervous system. Restless legs, mumbling, and stuttering developed in an elderly patient after increasing the dose of donepezil to 10 mg daily.[1] Symptoms resolved when donepezil was withdrawn and recurred on rechallenge.

1. Amouyal-Barkate K, *et al.* Abnormal movements with donepezil in Alzheimer disease. *Ann Pharmacother* 2000; **34:** 1347.

Effects on the urinary tract. Urinary incontinence is a recognised adverse effect of the older anticholinesterases such as neostigmine; not unexpectedly there have also been cases associated with donepezil.[1]

1. Hashimoto M, *et al.* Urinary incontinence: an unrecognised adverse effect with donepezil. *Lancet* 2000; **356:** 568.

Precautions

Donepezil and other acetylcholinesterase inhibitors should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction; their use is not recommended in patients recovering from bladder or gastrointestinal surgery. Care is also required in patients with a history of asthma, obstructive pulmonary disease, Parkinson's disease, or seizures, and in those, with, or at risk of developing, peptic ulcer disease. Patients with cardiovascular conduction disorders such as sick-sinus syndrome may be susceptible to the vagotonic effects of acetylcholinesterase inhibitors.

Dizziness, somnolence, fatigue, and muscle cramps may occur especially when starting treatment with or increasing the dose of acetylcholinesterase inhibitors; the performance of skilled tasks such as driving may be affected.

Interactions

As for Neostigmine, p.632. Hepatic metabolism of donepezil via the cytochrome P450 system has been demonstrated; plasma concentrations of donepezil may be raised by drugs that inhibit the isoenzyme CYP3A4 such as ketoconazole, itraconazole, and erythromycin, and by those that inhibit the isoenzyme CYP2D6 such as fluoxetine and quinidine. Conversely, plasma-donepezil concentrations may be reduced by enzyme inducers such as rifampicin, phenytoin, carbamazepine, and alcohol.

Antimuscarinics. Although antimuscarinics are expected to antagonise the effects of anticholinesterases, such combinations are sometimes used in patients with dementia who are distressed by symptoms of urge incontinence.[1] There have been, however, a few cases[2] of agitation, anxiety, confusion, aggression, and delusion precipitated by *tolterodine* in patients who had been stable on donepezil or rivastigmine. The interaction appeared to cause a state of cholinergic neurogenic hypersensitivity, similar to sudden withdrawal of the anticholinesterase.

1. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* 2004; **75:** 484–8.

2. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc* 2002; **50:** 1165–6.

Pharmacokinetics

Donepezil hydrochloride is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 hours after ingestion. It is about 95% bound to plasma proteins, mainly albumin. Donepezil undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. About 11% of a dose is present in plasma as 6-*O*-desmethyldonepezil, which has similar activity to the parent compound. Over 10 days, about 57% of a dose is recovered from the urine as unchanged drug and metabolites, and about 15% from the faeces; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 hours. Steady-state concentrations are achieved within 3 weeks of the start of therapy.

◊ References.

1. Tiseo PJ, *et al.* Metabolism and elimination of C-donepezil in healthy volunteers: a single-dose study. *Br J Clin Pharmacol* 1998; **46** (suppl 1): 19–24.

2. Reyes JF, *et al.* Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 9–17.

3. Nagy CF, *et al.* Steady-state pharmacokinetics and safety of donepezil HCl in subjects with moderately impaired renal function. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 18–24.

Uses and Administration

Donepezil hydrochloride, a piperidine derivative, is a reversible and selective inhibitor of acetylcholinesterase with actions similar to those of neostigmine (p.632). It is highly selective for the CNS and is used for the symptomatic treatment of dementia in Alzheimer's disease (below). In the UK, the licensed use of donepezil is limited to those patients with mild to moderately severe dementia; however, in the USA it is also licensed for use in those with severe symptoms.

Regardless of severity, donepezil hydrochloride is given in an initial oral dose of 5 mg once daily increased if necessary after 4 to 6 weeks to a maximum of 10 mg once daily; the dose should be taken just before bedtime. Clinical benefit should be reassessed on a regular basis.

In some countries, donepezil is also licensed for use in patients with vascular dementia (below); doses are similar to those used for the treatment of dementia in Alzheimer's disease.

Dementia. Donepezil hydrochloride is used in the symptomatic treatment of dementia in *Alzheimer's disease* (see Dementia, p.362). In individual studies, it appears to produce modest benefits in some patients with mild to moderately severe dementia.[1-4] These findings are also supported by a systematic review[5] which concluded that, for treatment periods of up to 1 year, donepezil produces modest improvements in cognitive function and global clinical state. Benefit has also been reported in patients with more severe dementia.[5-8] Although there are no comparative studies of donepezil and tacrine it has been suggested[9-11] that donepezil may prove preferable as it appears to be better tolerated and hepatotoxicity has not been reported to be a problem (but see Adverse Effects, above).

In the UK, NICE has recommended that treatment with donepezil should be limited to patients with moderate dementia and given under the following conditions:[12]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that donepezil could no longer be recommended in the treatment of mild dementia because its cost-effectiveness was questionable; however, it was recommended that those currently taking donepezil for mild dementia should continue on therapy until it was considered appropriate to stop.

Donepezil has also been tried in patients with *mild cognitive impairment*.[13,14] Findings from a double-blind study[14] have suggested that although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment when compared with placebo, the rate of progression after 3 years of therapy was not lower than that of the placebo group. The authors of a systematic review[15] of these 2 studies found no evidence to support the use of donepezil in patients with mild cognitive impairment. Any benefits were considered to be minor, short-lived, and associated with significant adverse effects.

Donepezil may be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[16] have shown an improvement in cognition and global function in patients with probable or possible vascular dementia. A systematic review also concluded that donepezil improved mild to moderate vascular cognitive impairment in the short term (treatment for 6 months).[17] The manufacturer has reported[18] that out of a total of 3 studies of donepezil in vascular dementia, one (Study 319) showed an apparently increased mortality compared with placebo: 1.7% and 0%, respectively. In a combined analysis of the other 2 studies, the mortality rate was 1.7% in the donepezil group and 2% in the placebo group. Combined analysis of all 3 studies showed no statistically significant difference in the mortality rates between the donepezil (1.7%) and placebo (1.1%) groups; the risk of vascular events such as stroke and myocardial infarction was also similar for each group. The unexpectedly low mortality rate with placebo in Study 319 was unusual given the age and pathology of the subjects. An increased risk of death has been reported with *galantamine* when used in patients who did not have Alzheimer's disease (see Effects on the Cardiovascular and Cerebrovascular Systems, p.366).

1. Rogers SL, *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50:** 136–45.

2. Mohs RC, *et al.* A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; **57:** 481–8.

3. Winblad B, *et al.* A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57:** 489–95.

4. Holmes C, *et al.* The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004; **63:** 214–19.

5. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 13/02/06).

6. Feldman H, *et al.* A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; **57:** 613–20.

7. Winblad B, *et al.* Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 2006; **367:** 1057–65.

8. Black SE, *et al.* Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology* 2007; **69:** 459–69.

9. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)

10. Shintani EY, Uchida KM. Donepezil: an anticholinesterase inhibitor for Alzheimer's disease. *Am J Health-Syst Pharm* 1997; **54:** 2805–10.

11. Barner EL, Gray SL. Donepezil use in Alzheimer disease. *Ann Pharmacother* 1998; **32:** 70–7.

12. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)

13. Salloway S, *et al.* Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004; **63:** 651–7.

14. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.

15. Birks J, Flicker L. Donepezil for mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 09/08/07).

16. Black S, *et al.* Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003; **34:** 2323–30.

17. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 13/02/06).

18. Eisai, Jpn. Eisai reports results from latest donepezil study in vascular dementia (issued 16th March, 2006). Available at: http://www.eisai.co.jp/enews/enews200609pdf.pdf (accessed 09/08/07)

Parkinsonism. Although acetylcholinesterase inhibitors such as donepezil hydrochloride may theoretically worsen parkinsonism symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p.954).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alzaimax; Cebrocal; Crialix; Cristaclar; Donepes; Donzeimer; Endoclar; Eranz; Lirpan; Oldinot; Onefin; Valpex; ***Austral.:*** Aricept; ***Austria:*** Aricept; ***Belg.:*** Aricept; ***Braz.:*** Eranz; ***Canad.:*** Aricept; ***Chile:*** Dazolin; Eranz; Evimal; ***Cz.:*** Aricept; Yasnal; ***Denm.:*** Aricept; ***Fin.:*** Aricept; ***Fr.:*** Aricept; ***Ger.:*** Aricept; ***Gr.:*** Aricept; ***Hong Kong:*** Aricept; ***Hung.:*** Aricept; ***India:*** Donaz; Donecept; ***Indon.:*** Alzim; Aricept; Fordesia; ***Irl.:*** Aricept; ***Israel:*** Aricept; Asenta; Memorit; ***Ital.:*** Aricept; Memac; ***Jpn:*** Aricept; ***Malaysia:*** Aricept; ***Mex.:*** Eranz; ***Norw.:*** Aricept; ***NZ:*** Aricept; ***Philipp.:*** Aricept; ***Pol.:*** Aricept; Cogiton; Donepex; Yasnal; ***Port.:*** Aricept; ***Rus.:*** Aricept (Арисепт); ***S.Afr.:*** Aricept; ***Singapore:*** Aricept; ***Spain:*** Aricept; ***Swed.:*** Aricept; ***Switz.:*** Aricept; ***Thai.:*** Aricept; ***Turk.:*** Aricept; ***UK:*** Aricept; ***USA:*** Aricept; ***Venez.:*** Eranz.

Galantamine Hydrobromide

(BANM, USAN, rINNM)

Galantamine, bromhydrate de; Galantamini hydrobromidum; Galanthamine Hydrobromide; Galanthamini Hydrobromidum; Hidrobromuro de galantamina. (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide.

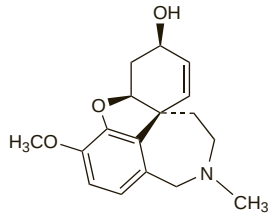
Галантамина Гидробромид

$C_{17}H_{21}NO_3,HBr$ = 368.3.

CAS — 357-70-0 (galantamine); 1953-04-4 (galantamine hydrobromide).

ATC — N06DA04.

ATC Vet — QN06DA04.



(galantamine)

Description. The hydrobromide of galantamine, an alkaloid which has been obtained from the Caucasian snowdrop (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related species.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Galantamine Hydrobromide). A white to almost white powder. Sparingly soluble in water; very slightly soluble in alcohol; soluble in 0.1N sodium hydroxide; insoluble in propyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p.364. Hypertension has also been reported with galantamine.

For details regarding dose adjustments in moderate hepatic or renal impairment, see under Uses and Administration, below. There are no data on the use of galantamine in patients with severe hepatic or renal impairment and consequently in the licensed product information it is contra-indicated in such patients; it should also not be given to patients with both significant hepatic and renal impairment.

Effects on the cardiovascular and cerebrovascular systems. Results from 2 studies of the use of galantamine in mild cognitive impairment (an unlicensed indication) have suggested that there may be an increased risk of death in patients given galantamine compared with those on placebo: out of a total of about 2000 patients, 13 died in the galantamine groups with only 1 death reported in the placebo groups.[1,2] About half of the deaths were caused by cardiovascular or cerebrovascular events.

For a suggestion of possibly increased mortality with *donepezil* in patients with vascular dementia, see Dementia, p.365.

1. Janssen-Ortho Inc. Safety information from investigational studies with Reminyl (galantamine hydrobromide) in mild cognitive impairment (MCI) (issued 18th April, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/reminyl_hpc-eng.pdf (accessed 05/08/08)
2. Ortho-McNeil Neurologics, Inc. Important prescribing information: deaths in subjects with mild cognitive impairment (MCI) (issued 31st March, 2005). Available at: http://www.fda.gov/medwatch/SAFETY/2005/reminylDDLmarch.pdf (accessed 14/02/06)

Interactions

As for Neostigmine, p.632. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Consequently its bioavailability may be increased by drugs that inhibit CYP2D6, such as quinidine, fluoxetine, fluvoxamine, and paroxetine, and by those that inhibit CYP3A4, such as ketoconazole and ritonavir. Dose reduction of galantamine may be required when given with such drugs.

Pharmacokinetics

Galantamine is well absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in about 1 hour after ingestion from conventional formulations; with modified-release formulations, peak concentrations occur about 4 to 5 hours after a dose and are somewhat lower. The absolute oral bioavailability of galantamine is about 90%. The presence of food delays the rate of absorption although the extent of absorption is not affected. Protein binding is about 18%. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; a number of active metabolites are formed. The elimination half-life is about 7 to 8 hours. After 7 days, the majority of a single oral dose is recovered in the urine with up to about 6% detected in the faeces; about 20 to 30% of the dose is excreted in the urine as unchanged galantamine. Clearance is reported to be 20% lower in females than in males and 25% lower in poor metabolisers than in extensive metabolisers.

◊ References.

1. Zhao Q, *et al.* Pharmacokinetics and safety of galantamine in subjects with hepatic impairment and healthy volunteers. *J Clin Pharmacol* 2002; **42:** 428–36.
2. Piotrovsky V, *et al.* Galantamine population pharmacokinetics in patients with Alzheimer's disease: modeling and simulations. *J Clin Pharmacol* 2003; **43:** 514–23.
3. Farlow MR. Clinical pharmacokinetics of galantamine. *Clin Pharmacokinet* 2003; **42:** 1383–92.

Uses and Administration

Galantamine hydrobromide is a reversible inhibitor of acetylcholinesterase activity, with actions similar to those of neostigmine (p.632). It also has an intrinsic action on nicotinic receptors. It is used in the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (below).

Galantamine is given as the hydrobromide although doses are expressed in terms of the base; 5.1 mg of galantamine hydrobromide is equivalent to about 4 mg of galantamine. An initial oral dose of 4 mg is given twice daily with food for 4 weeks, then increased to 8 mg twice daily. This dose should be maintained for at least 4 weeks; thereafter, the dose may be further increased to 12 mg twice daily according to response and tolerance. A modified-release preparation is also available for once-daily use. The clinical benefit of galantamine should be reassessed, preferably within the first 3 months, and thereafter on a regular basis. Reductions in dose may be necessary in patients with hepatic or renal impairment (see below) or in those also taking certain cytochrome P450 isoenzyme inhibitors (see Interactions, above).

Galantamine hydrobromide has also been used in various neuromuscular disorders, and to curtail the muscle relaxation produced by competitive neuromuscular blockers.

Administration in hepatic impairment. No dose adjustment is necessary in mild hepatic impairment. Patients with moderate impairment should begin with an oral dose of 4 mg once daily (or 8 mg every other day if using a modified-release preparation), preferably taken in the morning, for at least one week; thereafter the dose may be increased to 4 mg twice daily (or its once-daily equivalent if using a modified-release preparation) for at least 4 weeks, with subsequent increases up to a maximum of 8 mg twice daily (or its once-daily equivalent if using a modified-release preparation). Galantamine is contra-indicated in severe impairment (Child-Pugh Category C) due to lack of data.

Administration in renal impairment. UK licensed product information states that no dose adjustment is necessary in mild or moderate renal impairment. However, US licensed product information recommends that the dose should not exceed 16 mg daily in patients with moderate impairment.

Galantamine is contra-indicated in severe impairment (creatinine clearance less than 9 mL/minute) due to lack of data.

Dementia. Reviews[1-3] suggest that galantamine is of benefit in patients with mild to moderate symptoms of *Alzheimer's disease* (see Dementia, p.362); evidence in more severely impaired subjects is lacking. In the UK, NICE has recommended that the use of galantamine should be limited to patients with moderate dementia and given under the following conditions:[4]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that galantamine could no longer be recommended in the treatment of mild dementia because its cost-effectiveness was questionable; however, it was recommended that those currently taking galantamine for mild dementia should continue on therapy until it was considered appropriate to stop.

Galantamine may also be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[5] have shown a trend towards improved cognition in patients with probable vascular dementia, although patients numbers were too small for this to be significant. A more recent multicentre study[6] in patients with probable vascular dementia found cognitive improvement with galantamine to be greater than with placebo; however, improvement in daily activities with galantamine was similar to that seen with placebo.

A systematic review[3] concluded that galantamine could not be recommended for treatment in patients with *mild cognitive impairment* because of limited clinical benefit and an unexplained association with an excess death rate (see also Effects on the Cardiovascular and Cerebrovascular Systems, above).

1. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs* 2000; **60:** 1095–1122.
2. Pearson VE. Galantamine: a new Alzheimer drug with a past life. *Ann Pharmacother* 2001; **35:** 1406–13.
3. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/02/06).
4. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)
5. Erkinjuntti T, *et al.* Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; **359:** 1283–90.
6. Auchus AP, *et al.* Galantamine treatment of vascular dementia: a randomized trial. *Neurology* 2007; **69:** 448–58.

Preparations

USP 31: Galantamine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Intelec; Numencial; Reminyl; ***Austral.:*** Reminyl; ***Austria:*** Reminyl; ***Belg.:*** Reminyl; ***Braz.:*** Reminyl; ***Canad.:*** Reminyl; ***Chile:*** Reminyl; ***Cz.:*** Apo-Galant; Flashemel; Galamed; Kuroment; OxyGal; Reminyl; ZapTron; ***Denm.:*** Reminyl; ***Fin.:*** Reminyl; ***Fr.:*** Reminyl; ***Ger.:*** Reminyl; ***Gr.:*** Reminyl; ***Hong Kong:*** Reminyl; ***Hung.:*** Nivalin†; ***Indon.:*** Reminyl; ***Irl.:*** Reminyl; ***Israel:*** Reminyl; ***Ital.:*** Reminyl; ***Malaysia:*** Reminyl; ***Mex.:*** Reminyl; ***Neth.:*** Reminyl; ***Norw.:*** Reminyl; ***NZ:*** Reminyl; ***Philipp.:*** Reminyl; ***Pol.:*** Nivalin; Reminyl†; ***Port.:*** Reminyl; ***Rus.:*** Nivalin (Нивалин); Reminyl (Реминил); ***S.Afr.:*** Reminyl; ***Singapore:*** Reminyl; ***Spain:*** Reminyl; ***Swed.:*** Reminyl; ***Switz.:*** Reminyl; ***Thai.:*** Reminyl; ***Turk.:*** Reminyl; ***UK:*** Reminyl; ***USA:*** Razadyne; ***Venez.:*** Proneurax.

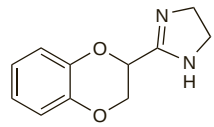
Idazoxan Hydrochloride *(BANM, pINNM)*

Hidrocloruro de idazoxano; Idazoxan, Chlorhydrate d'; Idazoxani Hydrochloridum; RX-781094. 2-(2,3-Dihydro-1,4-benzodioxin-2-yl)-2-imidazoline hydrochloride.

Идазоксана Гидрохлорид

$C_{11}H_{12}N_2O_2HCl$ = 240.7.

CAS — 79944-58-4 (idazoxan); 79944-56-2 (idazoxan hydrochloride).



(idazoxan)

Profile

Idazoxan hydrochloride is an alpha$_2$-adrenoceptor antagonist that has been investigated in neurological disorders including depression, dementia, and parkinsonism.

◊ References.

1. Ghika J, *et al.* Idazoxan treatment in progressive supranuclear palsy. *Neurology* 1991; **41:** 986–91.
2. Litman RE, *et al.* Idazoxan, an alpha2 antagonist, augments fluphenazine in schizophrenic patients: a pilot study. *J Clin Psychopharmacol* 1993; **13:** 264–7.
3. Grossman F, *et al.* A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. *J Affect Disord* 1999; **56:** 237–43.
4. Manson AJ, *et al.* Idazoxan is ineffective for levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2000; **15:** 336–7.
5. Rascol O, *et al.* Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease. *Mov Disord* 2001; **16:** 708–13.