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.

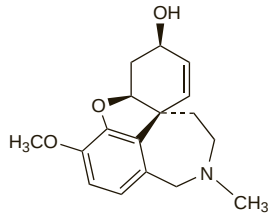
Галантамина Гидробромид

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

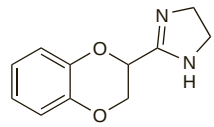
Idazoxan Hydrochloride *(BANM, pINNM)*

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.

Idebenone *(rINN)*

CV-2619; Idebenona; Idébénone; Idebenonum. 2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.

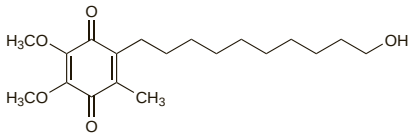
Идебенон

$C_{19}H_{30}O_5$ = 338.4.

CAS — 58186-27-9.

ATC — N06BX13.

ATC Vet — QN06BX13.



Profile

Idebenone has been used in the treatment of mental impairment associated with cerebrovascular disorders. A dose of 90 mg daily has been given orally in 2 divided doses after food. Idebenone has also been tried in Alzheimer's disease. It has also been investigated for the management of various clinical manifestations of Friedreich's ataxia and is used orally in a dose of 5 mg/kg daily in 3 divided doses for cardiomyopathy in this disease.

Idebenone is also available as a 1% cream for the cosmetic treatment of wrinkles.

Dementia. Idebenone was found to be safe and effective in patients with mild to moderate Alzheimer's disease (p.362) when followed for up to 2 years.[1,2] In a further study,[3] its safety and efficacy were comparable to tacrine. However, another study[4] found no clinically significant slowing of cognitive decline in patients with Alzheimer's disease treated with idebenone.

1. Weyer G, *et al.* Efficacy and safety of idebenone in the long-term treatment of Alzheimer's disease: a double-blind, placebo controlled multicentre study. *Hum Psychopharmacol Clin Exp* 1996; **11:** 53–65.
2. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm* 1998; **54** (suppl): 301–10.
3. Gutzmann H, *et al.* Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry* 2002; **35:** 12–18.
4. Thal LJ, *et al.* Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* 2003; **61:** 1498–1502.

Friedreich's ataxia. Preliminary studies of idebenone in the treatment of Friedreich's ataxia.[1-5]

1. Hausse AO, *et al.* Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 2002; **87:** 346–9.
2. Artuch R, *et al.* Friedreich's ataxia: idebenone treatment in early stage patients. *Neuropediatrics* 2002; **33:** 190–3.
3. Mariotti C, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; **60:** 1676–9.
4. Buyse G, *et al.* Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 2003; **60:** 1679–81.
5. Rustin P, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2004; **62:** 524–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Esanic; Geniceral; Idesole; Nemocebral; Pavertrin; Sicoplus; Ulcouro-na†; ***Ital.:*** Daruma†; Mnesis; ***Mex.:*** Lucebanol; ***Port.:*** Amizal; Cerestabon; Idecortex; ***Rus.:*** Noben (Нобен); ***Switz.:*** Mnesis; ***USA:*** Prevage.

Multi-ingredient: ***Arg.:*** Idesole Plus; Nemocebral Plus.

Memantine Hydrochloride

(BANM, USAN, rINNM)

1-Amino-3,5-dimethyladamantane Hydrochloride; D-145 (memantine); 3,5-Dimethyl-1-adamantanamine hydrochloride; DMAA (memantine); Hidrocloruro de memantina; Memantin Hidroklorür; Mémantine, Chlorhydrate de; Memantini Hydrochloridum. 3,5-Dimethyltricyclo[3.3.1.1.^{3,7}]decan-1-amine hydrochloride.

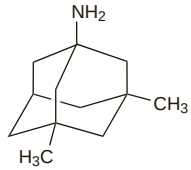
Мемантина Гидрохлорид

$C_{12}H_{21}N,HCl$ = 215.8.

CAS — 19982-08-2 (memantine); 41100-52-1 (memantine hydrochloride).

ATC — N06DX01.

ATC Vet — QN06DX01.



(memantine)

Adverse Effects and Precautions

Common adverse effects with memantine include constipation, dizziness, headache, hypertension, and somnolence. Less common reactions such as anxiety, hallucinations, confusion, fatigue, abnormal gait, hypertonia, vomiting, fungal infections, cystitis, thromboembolism, and increased libido have also occurred. Isolated cases of psychotic reactions and pancreatitis have been reported.

Dosage adjustment may be required in renal impairment, but recommendations vary, (see below).

Only limited clinical data are available for patients with recent myocardial infarction, uncompensated congestive heart failure, and uncontrolled hypertension and use of memantine in these patients should be closely monitored. Seizures have occurred rarely and caution is recommended in patients at risk of convulsions. Conditions that increase urinary pH, such as drastic changes in diet, renal tubular acidosis, or severe infections of the urinary tract, may decrease elimination of memantine resulting in increased plasma levels; patient monitoring is recommended in such cases.

Interactions

Use of other *N*-methyl-D-aspartate antagonists such as amantadine, ketamine, or dextromethorphan with memantine may increase both the incidence and severity of adverse effects and should be avoided. The effects of dopaminergics and antimuscarinics may also be enhanced whereas memantine may reduce the actions of barbiturates and antipsychotics.

Memantine may alter the effects of the antispasmodics baclofen and dantrolene. The clearance of memantine is reduced under alkaline urine conditions and drugs such as carbonic anhydrase inhibitors and sodium bicarbonate should be used with caution.

Pharmacokinetics

Memantine is well absorbed after oral doses. Peak plasma concentrations are achieved in about 3 to 8 hours. Plasma protein binding is about 45%. Memantine undergoes partial hepatic metabolism; the main metabolites include *N*-3,5-dimethyl-gludantan and 1-nitroso-3,5-dimethyl-adamantane. The majority of a dose is excreted unchanged via the kidney; some active renal tubular secretion and reabsorption occurs. The terminal half-life ranges from 60 to 100 hours although under alkaline conditions the rate of elimination is reduced.

◊ References.

1. Periclou A, *et al.* Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clin Pharmacol Ther* 2006; **79:** 134–43.
2. Kornhuber J, *et al.* Memantine pharmacotherapy: a naturalistic study using a population pharmacokinetic approach. *Clin Pharmacokinet* 2007; **46:** 599–612. Correction. *ibid.*; 712.

Uses and Administration

Memantine is a derivative of amantadine (p.792) and is likewise an antagonist of *N*-methyl-D-aspartate receptors. It is given in the treatment of moderate to severe Alzheimer's disease (see Dementia, below). Memantine has also been given in the treatment of parkinsonism and central spasticity, and in other disorders such as brain injury or comatose states. It is given orally as the hydrochloride.

In the treatment of **Alzheimer's disease**, the initial dose of memantine hydrochloride is 5 mg daily in the morning for the first week; this should be increased in weekly increments of 5 mg to a maximum dose of 20 mg daily. Doses of 10 mg daily and over should be taken in 2 divided doses. Dosage adjustment may be required in patients with renal impairment (see below). Clinical benefit should be reassessed on a regular basis.

Memantine hydrochloride has also been given by slow intravenous injection.

Memantine is under investigation in the treatment of glaucoma and peripheral neuropathy.

Administration in renal impairment. UK licensed product information advises that no dose adjustment is needed when memantine hydrochloride is given for Alzheimer's disease in patients with mild renal impairment (creatinine clearance [CC] 50 to 80 mL/minute). However, in those with moderate impairment (CC 30 to 49 mL/minute) a dose of 10 mg daily may be used (after starting at 5 mg daily) and if well tolerated after at least 7 days, it may be increased to 20 mg daily as described above (see above). In those with severe impairment (CC 5 to 29 mL/minute) the maximum daily dose is 10 mg. In the USA, licensed product information states that no dose reduction is required in those with mild or moderate impairment; a target dose of 10 mg daily is recommended in patients with severe impairment (CC 5 to 29 mL/minute).

Dementia. A systematic review[1] of the use of memantine in dementia (p.362) concluded that it did have a small beneficial effect on cognitive and functional decline at 6 months in patients with moderate to severe Alzheimer's disease; the effects were not clinically discernible in those with mild to moderate vascular dementia but were discernible in those with mild to moderate Alzheimer's disease. In the UK, NICE[2] has not recommended memantine in the treatment of patients with moderately severe to severe disease because of insufficient evidence of clinical effectiveness. A general review, including a safety profile, of memantine in Alzheimer's disease has also been published.[3]

1. McShane R, *et al.* Memantine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).
2. 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)
3. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. *Drugs* 2006; **66:** 1515–34.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Akatinol; Carrier; Conexine; Ebixa; Fentina; Lucidex; Merital; Neuroplus; Pronervon; ***Austral.:*** Ebixa; ***Austria:*** Axura; Ebixa; ***Belg.:*** Ebixa; ***Braz.:*** Alois; Ebix; ***Canad.:*** Ebixa; ***Chile:*** Ebixa; Eutebrol; Memax; Mimetix; ***Cz.:*** Akatinol†; Axura; Ebixa; ***Denm.:*** Ebixa; ***Fin.:*** Ebixa; ***Fr.:*** Ebixa; ***Ger.:*** Axura; Ebixa; ***Gr.:*** Ebixa; ***Hong Kong:*** Ebixa; ***Hung.:*** Ebixa; ***Irl.:*** Ebixa; ***Israel:*** Ebixa; Memox; ***Ital.:*** Ebixa; ***Mex.:*** Ebixa; Eutebrol; ***Neth.:*** Axura; Ebixa; ***Norw.:*** Ebixa; ***NZ:*** Ebixa; ***Philipp.:*** Abixa; ***Pol.:*** Axura; Ebixa; ***Port.:*** Axura; Ebixa; ***S.Afr.:*** Ebixa; ***Singapore:*** Ebixa; ***Spain:*** Axura; Ebixa; ***Swed.:*** Ebixa; ***Switz.:*** Axura; Ebixa; ***Thai.:*** Ebixa; ***Turk.:*** Ebixa; ***UK:*** Ebixa; ***USA:*** Namenda.

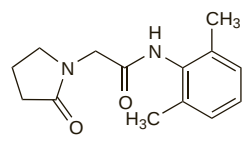
Nefiracetam *(rINN)*

DM-9384; DZL-221; Néfiracétam; Nefiracetamum. 2-Oxo-1-pyrrolidineaceto-2′,6′-xylidide.

Нефирацетам

$C_{14}H_{18}N_2O_2$ = 246.3.

CAS — 77191-36-7.



Profile

Nefiracetam acts on the CNS and has been described as a nootropic. It has been investigated in some cerebrovascular disorders and for the treatment of Alzheimer's disease.