Idebenone *(rINN)*

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

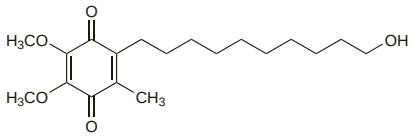
Идебенон

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

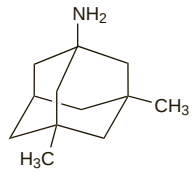
Мемантина Гидрохлорид

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

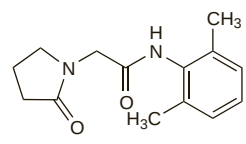
Nefiracetam *(rINN)*

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.