Idebenone *(rINN)*

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

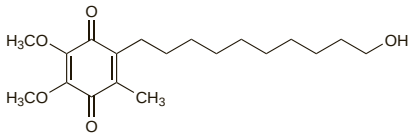
Идебенон

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

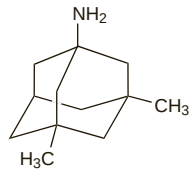
Мемантина Гидрохлорид

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

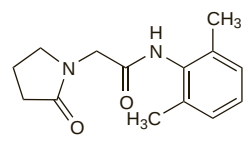
Nefiracetam *(rINN)*

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

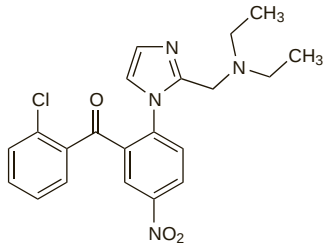
Nefiracetam acts on the CNS and has been described as a nootropic. It has been investigated in some cerebrovascular disorders and for the treatment of Alzheimer's disease.

Nizofenone *(rINN)*

Nizofenona; Nizofénone; Nizofenonum; Y-9179. 2′-Chloro-2-[2-[(diethylamino)methyl]imidazol-1-yl]-5-nitrobenzophenone.

Низофенон

$C_{21}H_{21}ClN_4O_3$ = 412.9.
CAS — 54533-85-6.
ATC — N06BX10.
ATC Vet — QN06BX10.



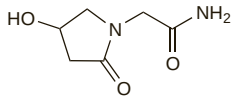
Profile
Nizofenone has been investigated as a nootropic and cerebral vasodilator. It has been used parenterally as the fumarate.

Oxiracetam *(BAN, rINN)*

CGP-21690E; CT-848; ISF-2522; Oksirasetaami; Oxiracétam; Oxiracetamum; Oxracetam. 4-Hydroxy-2-oxo-1-pyrrolidineacetamide.

Оксирацетам

$C_6H_{10}N_2O_3$ = 158.2.
CAS — 62613-82-5.
ATC — N06BX07.
ATC Vet — QN06BX07.



Profile
Oxiracetam has been used as a nootropic in organic brain syndromes and senile dementia.

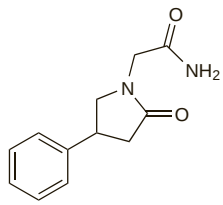
Dementia. Clinical benefit has been reported in patients with dementia (p.362) given oxiracetam,[1] but in the USA it was withdrawn from phase II clinical studies in patients with Alzheimer's disease due to lack of efficacy.[2]

1. Maina G, *et al*. Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. *Neuropsychobiology* 1990; **21**: 141–5.
2. Parnetti L. Clinical pharmacokinetics of drugs for Alzheimer's disease. *Clin Pharmacokinet* 1995; **29:** 110–29.

4-Phenylpiracetam ⊗

BRN-5030440; Carphedon; Karfedon. 2-Oxo-4-phenyl-1-pyrrolidineacetamide.

$C_{12}H_{14}N_2O_2$ = 218.3.
CAS — 77472-70-9.



Profile
4-Phenylpiracetam is a nootropic and has been used in the management of various cerebrovascular disorders. It has also been abused in sport.

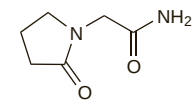
Preparations
Proprietary Preparations (details are given in Part 3)
Rus.: Phenotropil (Фенотропил).

Piracetam *(BAN, USAN, rINN)*

CI-871; Piracétam; Piracetamas; Piracetamum; Pirasetaami; Pirasetam; Pyrrolidone Acetamide; UCB-6215. 2-(2-Oxopyrrolidin-1-yl)acetamide.

Пирацетам

$C_6H_{10}N_2O_2$ = 142.2.
CAS — 7491-74-9.
ATC — N06BX03.
ATC Vet — QN06BX03.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Piracetam). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol. Protect from light.

Adverse Effects and Precautions
Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, and depression. Other reported adverse effects include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting, hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations, angioedema, and rashes. Piracetam should not be given to patients with hepatic impairment or severe renal impairment; dosage reduction is recommended for those with mild to moderate renal impairment. Therapy with piracetam should not be withdrawn abruptly in myoclonic patients due to the risk of inducing seizures. When used to treat cortical myoclonus, piracetam is contra-indicated in patients with cerebral haemorrhage, and should be used with caution after major surgery and in those with haemostatic disorders or severe haemorrhage.

Interactions
Anticoagulants. For reference to the effect of piracetam on *warfarin* therapy, see p.1431.

Pharmacokinetics
Piracetam is rapidly and extensively absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be 5 hours and it crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

Uses and Administration
Piracetam acts on the CNS and has been described as a nootropic; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin, and has also been used in dementia (see also below). Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo, cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

In cortical myoclonus, piracetam is given in oral doses of 7.2 g daily increasing by 4.8 g daily every 3 or 4 days up to a maximum of 20 g daily. It is given in 2 or 3 divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs. For dosage in renal impairment see below.

Piracetam has been given for various other disorders in a usual oral dose of up to 2.4 g daily in 2 or 3 divided doses; higher doses of up to 4.8 g daily have been used in severe cases. In severe disorders it has also been given by intramuscular or intravenous injection.

◊ General references.
1. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev* 2005; **11:** 169–82.

Administration in renal impairment. Dosage should be reduced in patients with mild to moderate renal impairment according to creatinine clearance (CC):
- CC between 50 and 79 mL/minute: two-thirds of the usual dose, given in 2 or 3 divided doses
- CC between 30 and 49 mL/minute: one-third of the usual dose, given in 2 divided doses
- CC between 20 and 29 mL/minute: one-sixth of the usual dose, given as a single dose
- CC less than 20 mL/minute: contra-indicated

Dementia. Although piracetam is used in some countries in the management of cognitive impairment and dementia (p.362), a systematic review[1] concluded that the evidence from the published literature did not support this use.

1. Flicker L, Grimley Evans J. Piracetam for dementia or cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/02/06).

Myoclonus. A review[1] of 62 case reports, 3 open studies, and 2 double-blind studies concluded that piracetam is beneficial in the treatment of disabling myoclonus (p.470), either as adjunctive treatment or as monotherapy. Similar conclusions were made in another review[2] in which experience of 12 patients with progressive myoclonus epilepsy, 8 of whom benefited from piracetam in doses of up to 45 g daily without significant adverse effects, was described.

1. Van Vleymen B, Van Zandijcke M. Piracetam in the treatment of myoclonus: an overview. *Acta Neurol Belg* 1996; **96:** 270–80.
2. Genton P, *et al*. Piracetam in the treatment of cortical myoclonus. *Pharmacopsychiatry* 1999; **32** (suppl): 49–53.

Stroke. Piracetam did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke in a multicentre, randomised, double-blind study,[1] although post hoc analyses suggested that it might confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate to severe degree. Further analyses of the same data concluded that piracetam did not produce significant adverse effects when given in high doses to patients with acute stroke,[2] and significantly more patients had recovered from aphasia on piracetam than placebo.[3] The results of two further randomised, double-blind, placebo-controlled studies supporting the role of piracetam as an adjunct to intensive speech therapy in improving aphasia following stroke were also reported.[3] In contrast, a systematic review including the first study considered that the trend towards an increased risk of early death in patients allocated to piracetam was of concern, and concluded that the data did not support routine use of piracetam in acute ischaemic stroke.[4]

1. De Deyn PP, *et al*. Treatment of acute and ischemic stroke with piracetam. *Stroke* 1997; **28:** 2347–52.
2. De Reuck J, Van Vleymen B. The clinical safety of high-dose piracetam—its use in the treatment of acute stroke. *Pharmacopsychiatry* 1999; **32** (suppl): 33–7.
3. Huber W. The role of piracetam in the treatment of acute and chronic aphasia. *Pharmacopsychiatry* 1999; **32** (suppl): 38–43.
4. Ricci S, *et al*. Piracetam for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).

Vertigo. Piracetam has been reported to be of benefit in patients with vertigo (p.565) of both central or peripheral origin.[1]

1. Oosterveld WJ. The effectiveness of piracetam in vertigo. *Pharmacopsychiatry* 1999; **32** (suppl): 54–60.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Noostan; ***Austria:*** Cerebryl; Nootropil; Novocephal; Pirabene; ***Belg.:*** Braintop; Docpirace; Geratam; Noodis; Nootropil; Piracemed; Piracetop; ***Braz.:*** Cintilan; Nootrofic†; Nootron; Nootropil; ***Chile:*** Nootropyl; ***Cz.:*** Cerebryl†; Geratam; Kalicor; Nootropil; Oikamid; Pirabene; ***Fin.:*** Nootropil; ***Fr.:*** Axonyl†; Gabacet; Geram†; Nootropyl; ***Ger.:*** Avigilen; Cerebroforte†; Cerepar N; Cuxabrain†; Memo-Puren†; Nootrop; Normabrain; Piracebral; Piracetrop; Sinapsan; ***Gr.:*** Aminotrophylle-88; Arterosol†; Cebragil; Latys; Lobelo; Meclivin†; Meditam†; Noforit; Nootrop; Oxynium; Piracem; Stamin; ***Hong Kong:*** Nootropil; Piratin; ***Hung.:*** Cerebryl; Lucetam; Memoril; Nootropil; Pirabene; Pyramen†; ***India:*** Nootropil; Normenta; Pirament; Piratam†; ***Indon.:*** Antikun; Benocetam; Cetoros; Chepamed; Ciclobrain; Encebion; Ethopil; Fepiram; Gotropil; Gracetam; Latropil; Lutrotam; Mersitropil; Neurocet; Neurotam; Noocephal; Nootropil; Nufacetam; Piratrof; Pratropil; Primatam; Procetam; Resibron; Revolan; Scantropil; Sotropil; Tropilex; ***Ital.:*** Cerebropan†; Nootropil; Norzetam†; Psycoton; ***Jpn:*** Myocalm; Nootropil; ***Malaysia:*** Cebrotonin†; Knowful; Nootropil; ***Mex.:*** Dinagen; Nootropil; ***Neth.:*** Nootropil; ***Norw.:*** Nootropil; ***Philipp.:*** Irahex; Nootropil; ***Pol.:*** Lucetam; Memotropil; Nootropil; ***Port.:*** Acetar; Noostan; Nootropil; Oxibran; Stimubral†; ***Rus.:*** Lucetam (Луцетам); Memotropil (Мемотропил); Nootropil (Ноотропил); Phezam (Фезам); Piratropil (Пиратропил); ***S.Afr.:*** Nootropil; ***Singapore:*** Cebrotonin; Cetam†; Nootropil; Piratam; Racetam; ***Spain:*** Ciclofalina; Nootropil; ***Swed.:*** Nootropil; ***Switz.:*** Nootropil; Pirax; ***Thai.:*** Embol; Mempil; Nocetam; Nootropil; Scarda; ***Turk.:*** Nootropil; Norotrop; ***UK:*** Nootropil; ***Venez.:*** Breinox; Nootropil†.

Multi-ingredient: ***Braz.:*** Energiclin; Energivit; Exit; Isketam; Vincetron†; ***Port.:*** Anacervix; Centracetam†; Euvifor†; Stimilfar†; ***Rus.:*** Omaron (Омарон); Piracezine (Пирацезин); Vinpotropile (Винпотропил); ***Spain:*** Anacervix; Devincal; Diemil; Piracetam Complex†; ***Venez.:*** Devincal†.