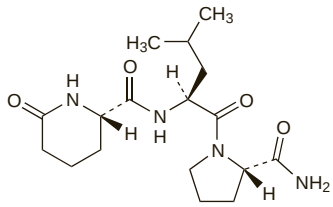
Posatirelin *(rINN)*

Posatirelina; Posatiréline; Posatirelinum; RGH-2202. (2*S*)-*N*[(1*S*)-1-[[(2*S*)-2-Carbamoyl-1-pyrrolidinyl]carbonyl]-3-methylbutyl]-6-oxopipecolamide.

Позатирелин

$C_{17}H_{28}N_4O_4$ = 352.4.

CAS — 78664-73-0.



Profile

Posatirelin is an analogue of protirelin (p.2175). It is claimed to have beneficial effects on CNS function, and has been investigated in the management of dementia of various causes.

◊ References.

1. Parnetti L, *et al.* Posatirelin for the treatment of late-onset Alzheimer's disease: a double-blind multicentre study vs citicoline and ascorbic acid. *Acta Neurol Scand* 1995; **92:** 135–40.
2. Parnetti L, *et al.* Posatirelin in the treatment of vascular dementia: a double-blind multicentre study vs placebo. *Acta Neurol Scand* 1996; **93:** 456–63.
3. Reboldi G, *et al.* Pharmacokinetic profile and endocrine effects of posatirelin treatment in healthy elderly subjects. *J Clin Pharmacol* 1996; **36:** 823–31.

Pramiracetam Sulfate *(USAN, rINNM)*

Amacetam Sulphate; CI-879; Pramiracétam, Sulfate de; Pramiracetam Sulphate; Pramiracetami Sulfas; Sulfato de pramiracetam. *N*-[2-(Diisopropylamino)ethyl]-2-oxo-1-pyrrolidineacetamide sulphate.

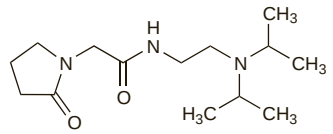
Прамирацетама Сульфат

$C_{14}H_{27}N_3O_2,H_2SO_4$ = 367.5.

CAS — 68497-62-1 (pramiracetam); 72869-16-0 (pramiracetam sulfate).

ATC — N06BX16.

ATC Vet — QN06BX16.



(pramiracetam)

Profile

Pramiracetam sulfate has been used in age-related memory impairment and senile dementia. It has also been tried, without much success, as an adjunct to ECT in severe depression.

◊ References.

1. McLean A, *et al.* Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia. *Brain Inj* 1991; **5:** 375–80.
2. Auteri A, *et al.* Pharmacokinetics of pramiracetam in healthy volunteers after oral administration. *Int J Clin Pharmacol Res* 1992; **12:** 129–32.
3. Scarpazza P, *et al.* Multicenter evaluation of pramiracetam for the treatment of memory impairment of probable vascular origin. *Adv Therapy* 1993; **10:** 217–25.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Neupramir†.

Pyritinol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de piritinol; Pirytynolu dichlorowodorek; Pyrithioxine Hydrochloride; Pyritinol, Chlorhydrate de; Pyritinoli Dihydrochloridum; Pyritinoli Hydrochloridum. 5,5-Dihydroxy-6,6-dimethyl-3,3-dithiodimethylenebis(4-pyridylmethanol) dihydochloride monohydrate.

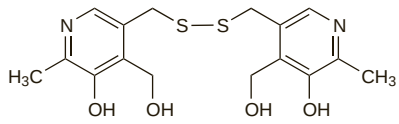
Пиритинола Гидрохлорид

$C_{16}H_{20}N_2O_4S_2,2HCl,H_2O$ = 459.4.

CAS — 1098-97-1 (pyritinol); 10049-83-9 (anhydrous pyritinol hydrochloride).

ATC — N06BX02.

ATC Vet — QN06BX02.



(pyritinol)

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Pyritinol hydrochloride has been described as a nootropic that promotes the uptake of glucose by the brain. It has been used in the treatment of various cerebrovascular and mental function disorders. It has been given in a usual oral dose of 600 mg daily in 3 divided doses. Pyritinol hydrochloride has also been given as an alternative to penicillamine in rheumatoid arthritis. It is also an ingredient of various preparations promoted as tonics.

◊ References.

1. Knezevic S, *et al.* Pyritinol treatment of SDAT patients: evaluation by psychiatric and neurological examination, psychometric testing and rCBF measurements. *Int Clin Psychopharmacol* 1989; **4:** 25–38.
2. Lemmel EM. Comparison of pyritinol and auranofin in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1993; **32:** 375–82.
3. Straumann A, *et al.* Acute pancreatitis due to pyritinol: an immune-mediated phenomenon. *Gastroenterology* 1998; **115:** 452–4.
4. Maria V, *et al.* Severe cholestatic hepatitis induced by pyritinol. *BMJ* 2004; **328:** 572–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Epocan†; ***Austria:*** Encephabol; ***Chile:*** Encefabol; ***Cz.:*** Encephabol; Enerbol; ***Ger.:*** Ardeyceryl P†; Encephabol; ***Hong Kong:*** Encephabol; ***Hung.:*** Enerbol†; ***India:*** Encephabol; ***Indon.:*** Encepan; Encephabol; Enerbol; ***Malaysia:*** Encephabol†; Pyritil; ***Mex.:*** Bonifen†; Encephabol; ***Philipp.:*** Encephabol; ***Port.:*** Bonifen†; Cerbon; ***Rus.:*** Encephabol (Энцефабол); Enerbol (Энербол); ***S.Afr.:*** Encephabol; ***Singapore:*** Encephabol†; ***Thai.:*** Encephabol; Memonol; Pyritil; ***Venez.:*** Acon; Bonifen; Bonitrop; Fitina; Garan†.

Multi-ingredient: ***Arg.:*** Gabimex Plus; ***Spain:*** Refulgin; Viadetres†.

Rivastigmine *(BAN, USAN, rINN)*

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Rivastigmiini; Rivastigmin; Rivastigmina; Rivastigminum; SDZ-212-713; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate). (–)-*m*-[(*S*)-1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate.

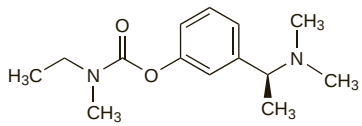
Ривастигмин

$C_{14}H_{22}N_2O_2$ = 250.3.

CAS — 123441-03-2.

ATC — N06DA03.

ATC Vet — QN06DA03.



Rivastigmine Hydrogen Tartrate *(BANM, rINNM)*

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Hidrogenotartrato de rivastigmina; Rivastigmine Bitartrate; Rivastigmine, Hydrogénotartrate de; Rivastigmine Tartrate; Rivastigmini Hydrogenotartras; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate).

Ривастигмина Гидротартрат

$C_{14}H_{22}N_2O_2.C_4H_6O_6$ = 400.4.

CAS — 129101-54-8.

ATC — N06DA03.

ATC Vet — QN06DA03.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p.364.

Effects on the gastrointestinal tract. A 67-year-old woman experienced severe vomiting after rivastigmine, in an oral dose of 4.5 mg, was mistakenly reintroduced without the recommended titration phase;[1] the vomiting was so severe that the patient also suffered a rupture of the oesophagus that needed corrective surgery. The authors' commented that careful dose titration of rivastigmine is necessary even when restarting treatment.

1. Babic T, *et al.* Spontaneous rupture of oesophagus (Boerhaave's syndrome) related to rivastigmine. *Age Ageing* 2000; **29:** 370–1.

Interactions

As for Neostigmine, p.632. See also Antimuscarinics, under Donepezil, p.365, for mention of an interaction between rivastigmine and tolterodine.

Pharmacokinetics

Rivastigmine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 1 hour after oral doses. Food delays absorption by about 1.5 hours and reduces maximum plasma concentrations. Absorption from transdermal patches is slow and peak plasma concentrations are reached in 10 to 16 hours after applying the first patch; with subsequent patches, peak concentrations are reached in about 8 hours. Exposure to rivastigmine is highest when the patch is applied to the upper back, chest, or upper arm, and about 20 to 30% lower when applied to the abdomen or thigh. Rivastigmine is about 40% bound to plasma proteins and readily crosses the blood-brain barrier; it is widely distributed throughout the body. Rivastigmine is rapidly and extensively metabolised, primarily by cholinesterase-mediated hydrolysis to the weakly active decarbamylated metabolite. The plasma half-life is about 1 hour after oral doses and about 3 hours after patch removal. After oral use, more than 90% of a dose is excreted in the urine within 24 hours; no unchanged rivastigmine is detected in the urine. Less than 1% of a dose appears in the faeces.

◊ References.

1. Hossain M, *et al.* Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. *Clin Pharmacokinet* 2002; **41:** 225–34.
2. Lefèvre G, *et al.* Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of body site application. *J Clin Pharmacol* 2007; **47:** 471–8.
3. Cummings J, *et al.* Pharmacokinetic rationale for the rivastigmine patch. *Neurology* 2007; **69** (suppl 1): S10–S13.
4. Lefèvre G, *et al.* Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients. *Clin Pharmacol Ther* 2008; **83:** 106–14.
5. Lefèvre G, *et al.* Pharmacokinetics and bioavailability of the novel rivastigmine transdermal patch versus rivastigmine oral solution in healthy elderly subjects. *J Clin Pharmacol* 2008; **48:** 246–52.

Uses and Administration

Rivastigmine is a carbamate type reversible acetylcholinesterase inhibitor; it also inhibits butyrylcholinesterase. Rivastigmine is selective for the CNS and is used for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (below) and idiopathic Parkinson's disease (below). It is given orally as the hydrogen tartrate or in transdermal patches as the base. For both routes doses are expressed in terms of the base; 2.4 mg of rivastigmine hydrogen tartrate is equivalent to about 1.5 mg of rivastigmine.

An initial oral dose is 1.5 mg given twice daily with food. Thereafter, the dose may be increased according to response and tolerance by increments of 1.5 mg twice daily at intervals of at least 2 weeks to a maximum dose of 6 mg twice daily. In the USA, licensed product information recommends dose increments at intervals of at least 4 weeks when treating dementia associated with Parkinson's disease.

Transdermal patches delivering 4.6 or 9.5 mg of rivastigmine over 24 hours are also available for once-daily application. In the USA, rivastigmine patches may be used for the treatment of dementia in Alzheimer's disease or Parkinson's disease; however, in the UK, use is restricted to dementia in Alzheimer's disease. An initial transdermal dose is 4.6 mg daily; after at least 4 weeks and if well tolerated, the dose should be increased to 9.5 mg daily. Patients already taking oral rivastigmine may be changed to the patches as follows:

- those taking 6 mg daily or less of oral rivastigmine may be switched to patches delivering 4.6 mg over 24 hours
- those taking more than 6 mg daily orally may be switched to patches delivering 9.5 mg over 24 hours