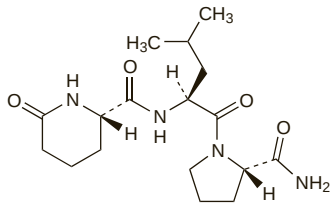
Posatirelin *(rINN)*

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.

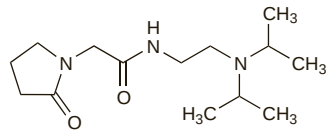
Прамирацетама Сульфат

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

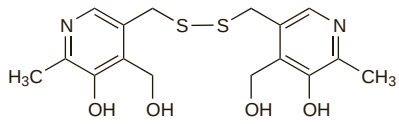
Пиритинола Гидрохлорид

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

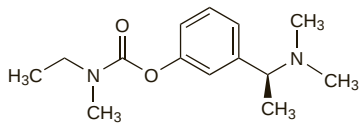
Ривастигмин

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

The first patch should be applied on the day following the last oral dose. The patch should be applied to intact skin on the upper or lower back, or on the upper arm or chest; it should not be applied to the abdomen or thigh due to decreased bioavailability. Re-application to the same site should be avoided for 14 days.

If treatment with oral or transdermal rivastigmine is interrupted for more than a few days, it should be restarted at the low initial dose, and then increased as described above. Clinical benefit should be reassessed on a regular basis; treatment should be stopped if there is no improvement after 3 months.

Dementia. Studies[1-4] and a systematic review[5] indicate that rivastigmine may be of benefit in the management of patients with mild to moderate dementia in *Alzheimer's disease* (see Dementia, p.362). In the UK, NICE has recommended that its use should be limited to patients with moderate dementia and given under the following conditions:[6]

- 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 rivastigmine 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 rivastigmine for mild dementia should continue on therapy until it was considered appropriate to stop.

Rivastigmine given in titrated doses of up to 6 mg twice daily was also found to be well tolerated, and to produce some improvement in behavioural and psychiatric symptoms, in a group of patients with *Lewy-body dementia*.[7] However, a systematic review[8] that included this study noted that rivastigmine did not have significant benefit in cognitive function compared with placebo; the authors considered that the evidence for its use in such patients was weak and that further trials were needed.

Rivastigmine has also been tried in the treatment of *vascular dementia*. A systematic review[9] concluded that although there is some evidence of benefit in these patients, available data are inadequate and further trials were warranted before rivastigmine could be recommended.

For the use of rivastigmine in the treatment of dementia in Parkinson's disease, see below.

1. Anand R, *et al.* Efficacy and safety results of the early phase studies with Exelon (ENA-713) in Alzheimer's disease: an overview. *J Drug Dev Clin Pract* 1996; **8:** 109–116.
2. Agid Y, *et al.* Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. *Curr Ther Res* 1998; **59:** 837–45.
3. Rösler M, *et al.* Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999; **318:** 633–8. Correction. *ibid.* 2001; **322:** 1456.
4. Winblad B, *et al.* IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology* 2007; **69** (suppl 1): S14–S22.
5. Birks J, *et al.* Rivastigmine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 14/02/06).
6. 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)
7. McKeith I, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; **356:** 2031–36.
8. Wild R, *et al.* Cholinesterase inhibitors for dementia with Lewy bodies. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 14/02/06).
9. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Parkinsonism. Although acetylcholinesterase inhibitors such as rivastigmine may theoretically worsen parkinsonian 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). In 2 large studies,[1,2] rivastigmine was found to produce some improvement in symptoms of dementia associated with Parkinson's disease when compared with placebo.

1. Emre M, *et al.* Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; **351:** 2509–18.
2. Wesnes KA, *et al.* Benefits of rivastigmine on attention in dementia associated with Parkinson disease. *Neurology* 2005; **65:** 1654–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Exelon; Remizeral; ***Austral.:*** Exelon; ***Austria:*** Exelon; ***Belg.:*** Exelon; ***Braz.:*** Exelon; Prometax; ***Canad.:*** Exelon; ***Chile:*** Exelon; Probrain; ***Cz.:*** Exelon; Prometax; ***Denm.:*** Exelon; ***Fin.:*** Exelon; ***Fr.:*** Exelon; ***Ger.:*** Exelon; ***Gr.:*** Exelon; Prometax; ***Hong Kong:*** Exelon; ***Hung.:*** Exelon; ***India:*** Exelon; ***Indon.:*** Exelon; ***Irl.:*** Exelon; ***Israel:*** Exelon; ***Ital.:*** Exelon; Prometax; ***Malaysia:*** Exelon; ***Mex.:*** Exelon; ***Neth.:*** Exelon; Prometax; ***Norw.:*** Exelon; ***NZ:*** Exelon; ***Philipp.:*** Exelon; ***Pol.:*** Exelon; ***Port.:*** Exelon; Prometax; ***Rus.:*** Exelon (Экселон); ***S.Afr.:*** Exelon; ***Singapore:*** Exelon; ***Spain:*** Exelon; Prometax; ***Swed.:*** Exelon; ***Switz.:*** Exelon; ***Thai.:*** Exelon; ***Turk.:*** Exelon; ***UK:*** Exelon; ***USA:*** Exelon; ***Venez.:*** Exelon.

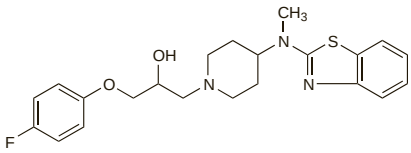
Sabeluzole *(BAN, USAN, rINN)*

R-58735; Sabeluzol; Sabéluzole; Sabeluzolum. (±)-4-(2-Benzothiazolylmethylamino)-α-[(4-fluorophenoxy)methyl]-1-piperidineethanol.

Сабелузол

$C_{22}H_{26}FN_3O_2S$ = 415.5.

CAS — 104153-38-0; 104383-17-7;.



Profile

Sabeluzole is a benzothiazole derivative with anticonvulsant and antihypoxic properties. It has been investigated in the treatment of Alzheimer's disease and of sleep apnoea.

Tacrine Hydrochloride

(BANM, USAN, rINNM)

Cl-970; Hidrocloruro de tacrina; Tacrine, chlorhydrate de; Tacrini hydrochloridum; Tetrahydroaminoacridine Hydrochloride; THA. 1,2,3,4-Tetrahydroacridin-9-ylamine hydrochloride.

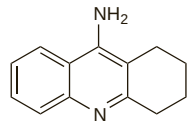
Такрина Гидрохлорид

$C_{13}H_{14}N_2$,HCl = 234.7.

CAS — 321-64-2 (tacrine); 1684-40-8 (tacrine hydrochloride).

ATC — N06DA01.

ATC Vet — QN06DA01.



(tacrine)

Pharmacopoeias. In *US* as the monohydrate.

USP 31 (Tacrine Hydrochloride). The monohydrate occurs as a white powder. Freely soluble in water, in alcohol, in dimethyl sulfoxide, in methyl alcohol, in propylene glycol, and in 0.1N hydrochloric acid; sparingly soluble in linoleic acid and in macrogol 400.

Adverse Effects and Treatment

As for Donepezil, p.364. Hepatotoxicity is common, and may be severe.

Effects on the CNS. Tonic or tonic-clonic seizures were reported in 6 of 78 patients given tacrine for mild or moderate dementia of the Alzheimer's type.[1]

1. Lebert F, *et al.* Convulsive effects of tacrine *Lancet* 1996; **347:** 1339–40.

Effects on the liver. Examination of data from 2446 patients who were at least 50 years old and received tacrine for Alzheimer's disease suggested that raised serum-alanine aminotransferase (ALT) concentrations are likely to occur in about 50% of patients.[1] Most cases developed within the first 12 weeks of therapy,[1] but an asymptomatic increase in ALT concentrations has been reported in a patient after more than 80 weeks of therapy.[2] The increase is usually asymptomatic and mild, and resolves upon dosage reduction or stopping treatment. However, a small percentage of patients may develop unpredictable life-threatening hepatotoxicity although frequent monitoring of ALT concentrations during the first 12 weeks of therapy can identify susceptible individuals. No significant correlation has been found between plasma-tacrine concentrations and hepatotoxicity.[3]

For guidelines on the monitoring of ALT concentrations during tacrine therapy, see Precautions, below.

1. Watkins PB, *et al.* Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; **271:** 992–8.
2. Terrell PS, *et al.* Late-onset alanine aminotransferase increase with tacrine. *Ann Pharmacother* 1996; **30:** 301.
3. Ford JM, *et al.* Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. *Clin Pharmacol Ther* 1993; **53:** 691–5.

Precautions

As for Donepezil, p.365. Tacrine should be used with care in patients with impaired liver function or who have a history of such impairment.

Serum-alanine aminotransferase (ALT) concentrations should be monitored in patients receiving continuous treatment with tacrine. Monitoring should be carried out every other week from at least week 4 to week 16 of therapy, and then every 3 months thereafter. Weekly monitoring is recommended in patients with ALT concentrations that are greater than twice the upper limit of the normal range.

If signs of liver involvement worsen, the dose should be reduced or the drug withdrawn. If a three- to five-fold increase of ALT concentrations occurs, a reduction in the dose by 40 mg daily is recommended. For greater increases in ALT, tacrine should be withdrawn. Treatment with tacrine may be restarted once signs of liver dysfunction return to normal; more frequent monitoring of liver enzyme values will be required. Withdrawal is also imperative in patients who develop jaundice, confirmed by elevated total bilirubin levels; such patients should not be treated again with tacrine.

Abruptly stopping tacrine therapy, or a large reduction in the dose, may be associated with behavioural disturbances and a decline in cognitive function.

Interactions

As for Neostigmine, p.632. Since tacrine is metabolised in the liver by the cytochrome P450 enzyme system (principally CYP1A2), drugs that either inhibit or induce the same isoenzymes may raise or lower plasma concentrations of tacrine, respectively. Tacrine may competitively inhibit the metabolism of other drugs that are also metabolised by the cytochrome P450 isoenzyme CYP1A2.

Antidepressants. *Fluvoxamine*, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, has increased plasma concentrations and reduced oral clearance of tacrine.[1]

1. Becquemont L, *et al.* Influence of the CYP1A2 inhibitor fluvoxamine on tacrine pharmacokinetics in humans. *Clin Pharmacol Ther* 1997; **61:** 619–27.

Antiparkinsonian drugs. Tacrine has been reported to exacerbate symptoms of parkinsonism and may therefore appear to reduce the effectiveness of *levodopa* therapy, see Antidementia drugs, p.807.

H_2-antagonists. *Cimetidine*, a non-specific inhibitor of the cytochrome P450 enzyme system, has been shown to inhibit the metabolism of tacrine resulting in reduced oral clearance and an increase in plasma concentrations.[1,2]

1. de Vries TM. Effect of cimetidine and low-dose quinidine on tacrine pharmacokinetics in humans. *Pharm Res* 1993; **10:** S337.
2. Forgue ST, *et al.* Inhibition of tacrine oral clearance by cimetidine. *Clin Pharmacol Ther* 1996; **59:** 444–9.

HRT. HRT with estradiol and levonorgestrel significantly increased tacrine plasma concentrations in all but one person in a study involving 10 healthy female subjects.[1] Metabolism of tacrine via the cytochrome P450 isoenzyme CYP1A2 was said to have been inhibited by the HRT.

1. Laine K, *et al.* Plasma tacrine concentrations are significantly increased by concomitant hormone replacement therapy. *Clin Pharmacol Ther* 1999; **66:** 602–8.

Tobacco smoking. Cigarette smoking can markedly reduce plasma-tacrine concentrations.[1]

1. Welty D, *et al.* The effect of smoking on the pharmacokinetics and metabolism of Cognex in healthy volunteers. *Pharm Res* 1993; **10:** S334.

Xanthines. For the effect of tacrine on the metabolism of *theophylline*, see p.1145.

Pharmacokinetics

Tacrine is rapidly absorbed from the gastrointestinal tract but large interindividual variations in oral bioavailability have been reported; peak plasma concentrations are achieved within 1 to 2 hours. Food reduces the absorption of tacrine by about 30 to 40%. It is about 55% bound to plasma proteins. Tacrine is subject to an extensive first-pass effect in the liver, and is metabolised by the cytochrome P450 system (principally CYP1A2) to several metabolites, the main one of which is the 1-hydroxy metabolite velnacrine. The elimination half-life is about 2 to 4 hours; little unchanged drug is excreted in the urine.