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.

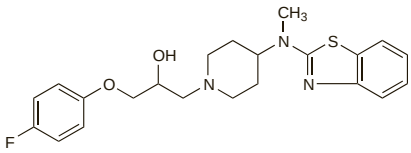
Sabeluzole *(BAN, USAN, rINN)*

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.

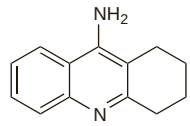
Такрина Гидрохлорид

$C_{13}H_{14}N_2$,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.

◊ In 3 studies in a total of 21 patients peak plasma concentrations of tacrine hydrochloride were achieved 0.5 to 3 hours after oral doses of 25 or 50 mg and oral bioavailability ranged from less than 5% to up to 36%.[1-3] Mean elimination half-lives were 1.37 and 1.59 hours after the 25 mg dose and 2.14 and 3.2 hours after the 50 mg dose. Tacrine's elimination appears to be mainly by metabolism in the liver and less than 3% of a dose was recovered unchanged in the urine of one patient.[1] Plasma concentrations of tacrine's main metabolite 1-hydroxy-9-aminotetrahydroacridine (velnacrine) rapidly exceed those of the parent compound and elimination half-lives of 43 and 81 minutes were found for this metabolite in 2 patients studied.[2] Tacrine's pharmacokinetics have been reviewed.[4]

1. Forsyth DR, *et al.* Pharmacokinetics of tacrine hydrochloride in Alzheimer's disease. *Clin Pharmacol Ther* 1989; **46:** 634–41.
2. Hartvig P, *et al.* Clinical pharmacokinetics of intravenous and oral 9-amino-1,2,3,4-tetrahydroacridine, tacrine. *Eur J Clin Pharmacol* 1990; **38:** 259–63.
3. Sitar DS, *et al.* Bioavailability and pharmacokinetic disposition of tacrine HCl in elderly patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **57:** 198.
4. Madden S, *et al.* Clinical pharmacokinetics of tacrine. *Clin Pharmacokinet* 1995; **28:** 449–57.

Uses and Administration

Tacrine hydrochloride is a centrally acting reversible inhibitor of acetylcholinesterase activity used in the treatment of mild to moderately severe dementia in Alzheimer's disease (below).

The initial oral dose of tacrine hydrochloride, expressed in terms of the base, is 10 mg four times a day for a minimum of 4 weeks. Dosage should not be increased during this period because the potential exists for a delay in onset of increased liver enzyme concentrations. Serum-alanine aminotransferase concentrations should be monitored regularly (see Precautions, above) and, if there is no significant increase, the daily dose may be increased by 40 mg at four-week intervals according to response and tolerance, to a maximum of 160 mg daily in four divided doses. Tacrine should be taken on an empty stomach to improve absorption, although it can be taken with food if gastrointestinal adverse effects are a problem.

Tacrine has been used intravenously to antagonise competitive neuromuscular blockers and as a postoperative respiratory stimulant.

Dementia. Tacrine is used in the symptomatic management of Alzheimer's disease (see Dementia, p.362). It may delay cognitive decline in some patients with mild or moderate Alzheimer's disease but many cannot tolerate the dosage required and have to stop treatment because of gastrointestinal effects or signs of hepatotoxicity. There have been numerous studies of the use of tacrine in Alzheimer's disease and a meta-analysis[1] found tacrine to have a small beneficial effect on both cognition and global clinical impression, although it was considered that the clinical relevance of these findings was unclear and that there were no data from long-term controlled studies. Some have considered[2-6] that a cautious trial of tacrine may be warranted in patients with mild to moderately severe Alzheimer's disease (although alternative drugs are now available) and various guidelines on its use have been issued.[5,6] The metabolite velnacrine has also been tried but does not appear to be effective, and is also associated with hepatotoxicity.[7]

1. Qizilbash N, *et al.* Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. *JAMA* 1998; **280:** 1777–82.
2. Crimson ML. Tacrine: first drug approved for Alzheimer's disease. *Ann Pharmacother* 1994; **28:** 744–51.
3. Davis KL, Powchik P. Tacrine. *Lancet* 1995; **345:** 625–30.
4. Samuels SC, Davis KL. A risk-benefit assessment of tacrine in the treatment of Alzheimer's disease. *Drug Safety* 1997; **16:** 66–77.
5. Lyketsos CG, *et al.* Guidelines for the use of tacrine in Alzheimer's disease: clinical application and effectiveness. *J Neuropsychiatr Clin Neurosci* 1996; **8:** 67–73.
6. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
7. Birks J, Wilcock GGW. Velnacrine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Preparations

USP 31: Tacrine Capsules.

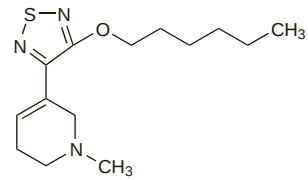
Proprietary Preparations (details are given in Part 3)
Arg.: Cognitiv†; ***Austral.:*** THA; ***Braz.:*** Tacrinal†; ***Gr.:*** Cognex†; ***Spain:*** Cognex†; ***USA:*** Cognex.

Xanomeline *(USAN, rINN)*

LY-246708; NNC-11-0232; Xanomelina; Xanoméline; Xanomelinum. 3-[4-(Hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridine.

Ксаномелин

$C_{14}H_{23}N_3OS$ = 281.4.
CAS — 131986-45-3.



Profile

Xanomeline is a selective muscarinic M_1 agonist. Xanomeline tartrate has been studied in the management of Alzheimer's disease but drugs of this type have not generally produced benefit.

◊ References.

1. Sramek JJ, *et al.* The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol* 1995; **35:** 800–806.
2. Bodick NC, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54:** 465–73.