Adverse Effects and Precautions

As for Bromocriptine, p.798. Reactions may occur at the site of application and are usually mild or moderate in intensity. The site should be rotated on a daily basis and the same site should not be used within 14 days.

Licensed product information recommends that rotigotine should be used with caution in patients with severe hepatic impairment and reduced doses may be necessary in cases of worsening impairment; however, this is based on a lack of evidence in such patients.

Interactions

Since it is a dopamine agonist, rotigotine may share some of the pharmacological interactions of bromocriptine, p.800.

Caution is advised when other sedating drugs or alcohol are used with rotigotine because of possible additive effects.

Pharmacokinetics

Rotigotine has poor oral bioavailability as it undergoes extensive first-pass metabolism via glucuronidation in the gut wall and liver. Peak plasma concentrations are achieved 24 hours after transdermal application. Steady-state concentrations are reached after 24 to 48 hours of continuous daily application. It undergoes *N*-dealkylation and conjugation to form inactive metabolites. Rotigotine is excreted mainly in the urine and about 23% appears in the faeces. The elimination half-life is 5 to 7 hours. It is distributed into milk of *rats*.

Uses and Administration

Rotigotine is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p.798), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. It is used as monotherapy in the management of Parkinson's disease (p.791), mainly in the early stage. It may also be used as an adjunct to levodopa therapy. Rotigotine is given as transdermal patches delivering amounts ranging from 2 to 8 mg per 24 hours.

When given as *monotherapy*, the initial dose is 2 mg daily, increased in weekly steps of 2 mg if necessary to a maximum of 8 mg daily.

Rotigotine may also be used as *adjunctive therapy* with levodopa in an initial dose of 4 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 16 mg daily.

Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Treatment with rotigotine should be withdrawn gradually; the daily dose should be reduced in steps of 2 mg every other day until complete withdrawal is achieved.

Rotigotine is also being studied as a transdermal preparation in the treatment of restless legs syndrome.

◊ References.

1. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003; **60:** 1721–8.
2. Stiasny-Kolster K, *et al*. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov Disord* 2004; **19:** 1432–8.
3. Poewe W, Leussi F. Clinical studies with transdermal rotigotine in early Parkinson's disease. *Neurology* 2005; **65** (suppl 1): S11–S14. Correction. *ibid.*; 1328.
4. Watts RL, *et al*. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 2007; **68:** 272–6. Correction. *ibid.*; **69:** 617.
5. Splinter MY. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. *Ann Pharmacother* 2007; **41:** 285–95.
6. LeWitt PA, *et al*. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 2007; **68:** 1262–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Neupro; ***Gr.:*** Neupro; ***Pol.:*** Neupro; ***Port.:*** Neupro; ***UK:*** Neupro; ***USA:*** Neupro†.

Selegiline Hydrochloride

(BANM, USAN, rINNM) ⊗

Deprenyl; L-Deprenyl; Hidrocloruro de selegilina; Selegiliinihydrokloridi; Selegilin Hidroklorür; Selegilin hydrochlorid; Sélégiline, chlorhydrate de; Selegilinhydroklorid; Selegilini hydrochloridum; Selegilino hidrochloridas; Szelegilin-hidroklorid. (–)-(*R*)-*N*,α-Dimethyl-*N*-(prop-2-ynyl)phenethylamine hydrochloride; (*R*)-Methyl(α-methylphenethyl)prop-2-ynylamine hydrochloride.

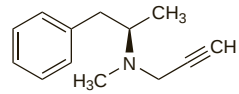
Селегилина Гидрохлорид

$C_{13}H_{17}N,HCl$ = 223.7.

CAS — 14611-51-9 (selegiline); 2079-54-1 (selegiline hydrochloride); 14611-52-0 (selegiline hydrochloride).

ATC — N04BD01.

ATC Vet — QN04BD01.



(selegiline)

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Selegiline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in acetone. A 2% solution in water has a pH of 3.5 to 4.5. Protect from light.
USP 31 (Selegiline Hydrochloride). A white, odourless crystalline powder. Freely soluble in water, in chloroform, and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects

Selegiline is often given as an adjunct to levodopa therapy and many of the adverse effects reported may be attributed to enhanced levodopa activity; dosage of levodopa may have to be reduced. However, most reported adverse effects, with the possible exception of increased dyskinesias and cardiac arrhythmias, have also been seen with selegiline monotherapy. Adverse effects have included orthostatic hypotension, chest pain, nausea, vomiting, constipation, diarrhoea, confusion, headache, tremor, vertigo, dizziness, psychosis, depression, hallucinations, agitation, dry mouth, sore throat, difficulty in micturition, skin reactions, back pain, muscle cramps, joint pain, and myopathy. The amfetamine metabolites of selegiline may cause insomnia and abnormal dreams; evening doses should be avoided. Transient increases in liver enzymes have been reported. Mouth ulcers and stomatitis may occur with the oral lyophilisate.

Since the selectivity of selegiline is lost at higher doses, signs and symptoms of overdosage may resemble those of non-selective MAOIs such as phenelzine (see p.415).

Effects on carbohydrate metabolism. Profound hypoglycaemia developed in a 70-year-old man after selegiline was added to his existing medication for Parkinson's disease.[1] Hypoglycaemia was accompanied by hyperinsulinaemia and resolved 1 week after stopping selegiline.

1. Rowland MJ, *et al.* Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J Clin Pharmacol* 1994; **34:** 80–5.

Effects on mortality. For reference to a study which observed an increased mortality rate in patients with Parkinson's disease taking selegiline and levodopa compared with those taking levodopa alone, see Parkinsonism under Uses and Administration, below.

Precautions

Selegiline should be used with caution in patients with a history of peptic ulceration and avoided in those with active ulceration. It should also be used with caution in uncontrolled hypertension, arrhythmias, angina, severe liver or kidney dysfunction, or psychosis.

Cardiovascular disorders. An investigation[1] of the autonomic effects of selegiline as a potential cause of the unexpected mortality observed in a study[2] in patients with Parkinson's disease receiving selegiline and levodopa (see Parkinsonism, below) suggested that the risk of orthostatic hypotension with this combination may have been underestimated. It was considered prudent to withdraw selegiline from those with symptomatic orthostatic hypotension or cardiovascular or cerebrovascular disease. For those without symptomatic morbidity, but a greater than 20 mmHg fall in blood pressure on standing for 2 minutes, gradual withdrawal of selegiline with adjustment of levodopa dosage should be considered.

1. Churchyard A, *et al.* Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **63:** 228–34.
2. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.

Interactions

Selegiline is less likely than non-selective MAOIs, such as phenelzine, to interact with tyramine in food; such hypertensive reactions have been reported rarely at usual doses but UK licensed product information for oral formulations states that its selectivity is lost at higher doses and it must be assumed that selegiline can usually only be used safely without dietary restrictions at doses of up to 10 mg daily. US licensed information for the transdermal preparation states that dietary restrictions are necessary at doses of 9 mg daily and above. For dietary restrictions applicable to patients taking MAOIs, see p.417.

Even when given in therapeutic doses life-threatening interactions can occur between selegiline and pethidine. Serious reactions, sometimes fatal, have also been reported when selegiline was used with tricyclic antidepressants or serotonin reuptake inhibitors including the SSRIs and venlafaxine. Licensed drug information states that 14 days should elapse between stopping selegiline and starting treatment with tricyclic or serotonergic antidepressants. Conversely, selegiline should not be given to patients who have recently received these antidepressants; at least 5 weeks should elapse between stopping fluoxetine and starting treatment with selegiline. Use of selegiline with non-selective MAOIs may cause severe hypotension and such use is not recommended.

Antidepressants. Although there have been studies in which patients with parkinsonism have received selegiline with *SSRIs* such as fluoxetine[1] or paroxetine[2] (apparently without any problems) there have been reports of reactions[3-5] such as shivering and sweating, hypertension, hyperactivity, and ataxia occurring when selegiline and fluoxetine have been used together. The FDA noted[6] that reactions similar to those between SSRIs and non-selective MAOIs had also been reported in patients taking selegiline with paroxetine or sertraline.

Severe reactions, sometimes fatal, have also occurred in patients taking selegiline and *tricyclic antidepressants*.[6] For a report of serotonin syndrome developing when *venlafaxine* was given after selegiline (despite a drug-free period) see p.429.

There has been a report[7] of a patient receiving the non-selective MAOI *iproniazid* who experienced severe orthostatic hypotension when given selegiline. Selegiline given with the reversible MAOI *moclobemide* to healthy subjects markedly increased the pressor response to tyramine compared with the effects of each drug used alone.[8] The authors concluded that dietary restriction of tyramine-containing foods would be necessary if these drugs were to be used together.

One UK manufacturer (*Cephalon, UK*) states that oral selegiline should not be given with any type of antidepressant, while another (*Orion, UK*) advises that use with SSRIs or venlafaxine be avoided and recommends caution when used with the tricyclics. The US manufacturer of transdermal selegiline (*Bristol-Myers Squibb, USA*), used for depression, states that use with other antidepressants such as *bupropion*, *mirtazapine*, serotonin reuptake inhibitors, *St John's wort*, and tricyclics is contra-indicated.

1. Waters CH. Fluoxetine and selegiline—lack of significant interaction. *Can J Neurol Sci* 1994; **21:** 259–61.
2. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* 1994; **28:** 405–6.
3. Suchowersky O, de Vries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990; **35:** 571–2.
4. Jermain DM, *et al.* Potential fluoxetine-selegiline interaction. *Ann Pharmacother* 1992; **26:** 1300.
5. Montastruc JL, *et al.* Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* 1993; **341:** 555.
6. Anonymous. Eldepryl and antidepressant interaction. *FDA Med Bull* 1995; **25** (Feb.): 6.
7. Pare CMB, *et al.* Attempts to attenuate the 'cheese effect': combined drug therapy in depressive illness. *J Affect Disord* 1985; **9:** 137–41.
8. Korn A, *et al.* Tyramine pressor sensitivity in healthy subjects during combined treatment with moclobemide and selegiline. *Eur J Clin Pharmacol* 1996; **49:** 273–8.

Antimigraine drugs. Some serotonin agonists including *rizatriptan*, *sumatriptan*, and *zolmitriptan* are metabolised via monoamine oxidase type A and therefore it is considered unlikely that selegiline, a monoamine oxidase type B inhibitor, would interact with these drugs. Nevertheless, one manufacturer (*Cephalon, UK*) of oral selegiline contra-indicates its use in patients also receiving serotonin agonists; it is also recommended that at least 24 hours should elapse between stopping selegiline and starting treatment with these drugs.

Opioid analgesics. Selegiline can produce life-threatening reactions when given with *pethidine*.[1]

Some manufacturers contra-indicate use of selegiline with pethidine and other opioid analgesics such as *dextropropoxyphene*, *methadone*, and *tramadol*.

1. Zornberg GL, *et al*. Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.*; 440.

Oral contraceptives. The total area under the concentration-time curve for selegiline given in single doses of 5 to 40 mg was raised ten- to twentyfold in 4 women who were using oral hormonal contraceptives when compared with 4 women receiving

no other medication.[1] It was suggested that use of selegiline and oral hormonal contraceptives should be avoided or the dosage of selegiline reduced.

1. Laine K, *et al.* Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol* 1999; **47:** 249–54.

Sympathomimetics. Licensed information for a US product (*Eldepryl; Somerset, USA*) states that there has been a report of hypertensive crisis in a patient taking recommended doses of selegiline and *ephedrine*. A hypertensive reaction after low-dose *dopamine* infusion has been reported[1] in a 75-year-old patient taking selegiline 10 mg daily for Parkinson's disease. The authors suggest that this may indicate a non-specific action of selegiline at usual doses on peripheral monoamine oxidase type-A. UK licensed product information states that dopamine should be used with caution in patients taking selegiline.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Pharmacokinetics

Selegiline is readily absorbed from the gastrointestinal tract and peak plasma concentrations are achieved in 30 minutes after oral doses of conventional preparations. Although subject to large interindividual variation, bioavailability is about 10% and is increased when given with food. Selegiline is rapidly distributed throughout the body and crosses the blood-brain barrier. It undergoes extensive first-pass metabolism in the liver to produce at least 5 metabolites, including *l*-(−)-desmethylselegiline (norselegiline), *l*-(−)-*N*-methylamfetamine, and *l*-(−)-amfetamine. Plasma concentrations of selegiline metabolites are greatly reduced after doses of the oral lyophilisate preparation, the majority of which undergoes absorption through the buccal mucosa. Selegiline is excreted as metabolites mainly in the urine and about 15% appears in the faeces. At steady state the elimination half-life is reported to be 10 hours.

◊ References.

1. Heinonen EH, *et al.* Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites. *Clin Pharmacol Ther* 1994; **56:** 742–9.
2. Mahmood I, *et al.* Clinical pharmacokinetics and pharmacodynamics of selegiline: an update. *Clin Pharmacokinet* 1997; **33:** 91–102.
3. Anttila M, *et al.* Marked effect of liver and kidney function on the pharmacokinetics of selegiline. *Clin Pharmacol Ther* 2005; **77:** 54–62.
4. Azzaro AJ, *et al.* Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. *J Clin Pharmacol* 2007; **47:** 1256–67.

Uses and Administration

Selegiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease mainly as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response, but see Parkinsonism, below. Addition of selegiline to levodopa therapy may enable the dosage of levodopa to be reduced by about 10 to 30%. Selegiline may be given alone in early Parkinson's disease in an attempt to delay the need for levodopa therapy. It is also used in the treatment of depression (see also below).

In the treatment of **Parkinson's disease**, selegiline hydrochloride is given by mouth as conventional preparations such as capsules, tablets, or liquid, or as lyophilisate tablets. The dose of the conventional preparations is 10 mg daily, either as a single dose in the morning or in 2 divided doses of 5 mg at breakfast and lunchtime. The initial dose of the oral lyophilisate tablets is 1.25 mg daily at least 5 minutes before breakfast; patients already receiving 10 mg of conventional preparations can be transferred to 1.25 mg of the oral lyophilisate. In the USA, the initial oral lyophilisate dose of 1.25 mg daily may be increased, after at least 6 weeks, to 2.5 mg given once daily, if necessary.

To avoid initial confusion and agitation, particularly in the elderly, the *BNF* suggests it may be appropriate when using conventional preparations to start treatment with a dose of 2.5 mg daily.

In the USA, transdermal patches delivering 6, 9, or 12 mg of selegiline over 24 hours are available for the treatment of **depression**. The initial dose is 6 mg daily, increased in steps of 3 mg every 2 weeks if necessary, to a maximum of 12 mg daily. Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Dose increases should be made with caution in the elderly and patients should be closely observed for postural changes in blood pressure during treatment. Dietary restrictions are necessary at doses of 9 mg daily and above, see p.417.

Other conditions in which selegiline has been tried include dementia.

◊ Some references to the actions of selegiline.

1. Youdim MBH, Finberg JPM. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine oxidase B inhibitors. *Clin Pharmacol Ther* 1994; **56:** 725–33.
2. Lange KW, *et al.* Biochemical actions of l-deprenyl (selegiline). *Clin Pharmacol Ther* 1994; **56:** 734–41.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; selegiline is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (p.1860).

References.

1. Houtsmuller EJ, *et al.* Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* 2004; **172:** 31–40.

Dementia. The hypothesis that neurodegeneration in Alzheimer's disease (p.362) might be due to free radical formation has led to drugs such as selegiline being tried as antoxidant therapy.

Early double-blind studies[1,2] indicated that oral selegiline 10 mg daily might produce beneficial effects in patients with Alzheimer's disease but it was suggested that improvements in mood and cognitive function may have been due to a reduction in tension and depression.[3] A 15-month study in Alzheimers's patients with mild cognitive impairment showed oral selegiline 10 mg daily to have little effect,[4] although the authors pointed out that those with more severe dementia have shown more response in other studies. The conclusion of a later study[5] that oral selegiline 10 mg daily slowed progression in patients with moderate disease has been criticised[6] on the grounds that any effect was only evident after statistical adjustment to the original analysis. In addition a systematic review[7] examining the effects of selegiline concluded that there was no meaningful evidence of a beneficial effect of oral selegiline in patients with Alzheimer's disease. They also considered that there was no longer any justification for its use in patients with Alzheimer's disease.

1. Piccinin GL, *et al.* Neuropsychological effects of -deprenyl in Alzheimer's type dementia. *Clin Neuropharmacol* 1990; **13:** 147–63.
2. Mangoni A, *et al.* Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. *Eur Neurol* 1991; **31:** 100–107.
3. Anonymous. Drugs for Alzheimer's disease. *Drug Ther Bull* 1990; **28:** 42–4.
4. Burke WJ, *et al.* L-Deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. *J Am Geriatr Soc* 1993; **41:** 1219–25.
5. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
6. Pincus MM. Alpha-tocopherol and Alzheimer's disease. *N Engl J Med* 1997; **337:** 572.
7. Birks J, Flicker L. Selegiline for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).

Depression. Selegiline is a selective inhibitor of monoamine oxidase type B and there are reports[1-3] of it producing improvement in depression (p.373). However, at the doses usually required to produce an antidepressant effect the specificity of oral selegiline is reported to be lost and it has been suggested that the efficacy of selegiline as an antidepressant might depend on inhibition of monoamine oxidase A rather than inhibition of monoamine oxidase B alone. Such a loss of specificity would mean that patients taking selegiline for depression would need to observe the dietary restrictions applicable to non-selective MAOIs.

To overcome the problems associated with the oral route, transdermal selegiline has also been tried and may be more effective than placebo in the treatment of depression.[4] The use of the transdermal route allows sustained blood levels of selegiline to be delivered without extensive inhibition of peripheral monoamine oxidase A. Transdermal patches of selegiline are licensed for the treatment of depression in the USA.

1. Mendlewicz J, Youdim MBH. L-Deprenil, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. *Br J Psychiatry* 1983; **142:** 508–11.
2. Mann JJ, *et al.* A controlled study of the antidepressant efficacy and side-effects of (−)-deprenyl. *Arch Gen Psychiatry* 1989; **46:** 45–50.
3. Sunderland T, *et al.* High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry* 1994; **51:** 607–15.
4. Frampton JE, Plosker GL. Selegiline transdermal system: in the treatment of major depressive disorder. *Drugs* 2007; **67:** 257–65.

Narcoleptic syndrome. Small controlled studies[1,2] have suggested that oral selegiline 20 to 40 mg daily has a beneficial effect on symptoms of narcolepsy and cataplexy (p.2148); at such a dosage a low-tyramine diet is considered necessary.

1. Hublin C, *et al.* Selegiline in the treatment of narcolepsy. *Neurology* 1994; **44:** 2095–2101.
2. Mayer G, *et al.* Selegeline [sic] hydrochloride treatment in narcolepsy: a double-blind, placebo-controlled study. *Clin Neuropharmacol* 1995; **18:** 306–19.

Parkinsonism. As a selective monoamine oxidase type B inhibitor, selegiline reduces the metabolism of dopamine and thereby enhances its actions. It reduces levodopa's 'end-of-dose' effect and has a dose-sparing effect. Some have used it as **monotherapy** in an attempt to delay the need for levodopa. If progression of Parkinson's disease (p.791) were due to a cytotoxic effect of free radicals, generated during the metabolism of dopamine, on dopaminergic neurones in the substantia nigra, selegiline might slow the process by reducing their formation. In a large early study,[1] the DATATOP study, selegiline monotherapy delayed the need to start levodopa in patients with early Parkinson's disease. These findings were corroborated by other smaller studies.[2,3] There has been much debate over whether the benefit was due to a neuroprotective or symptomatic effect. Re-analysis of the DATATOP data by independent workers[4,5] and findings of other studies[6] supported a symptomatic effect. Subsequent studies involving DATATOP patients were also consistent with a symptomatic effect; any benefit produced by selegiline appeared to be less pronounced as the duration of treatment increased[7] and was lost completely long term.[8,9] However, a later study[10] designed to minimise any symptomatic effect cast doubt on whether the delay in progression of the signs and symptoms of Parkinson's disease obtained with selegiline was entirely due to a symptomatic effect.

Studies of the use of selegiline as an **adjunct** to levodopa therapy[6,11,12] indicate that selegiline permits a modest reduction in the dosage requirements of levodopa. An interim analysis of a study of the early addition of selegiline to levodopa has also suggested that selegiline might stabilise the long-term daily levodopa dosage.[13] As with monotherapy, combined therapy has been reported to slow symptom progression.[14]

The use of selegiline in Parkinson's disease has been questioned after a UK study[11] found an unexpected increase in mortality in patients taking levodopa with selegiline compared with those taking levodopa alone. No difference in mortality had been detected at the 3-year follow-up[15] but after an average follow-up time of 5.6 years[11] mortality was 60% higher in the group also receiving selegiline. The study has been criticised on many grounds including the fact that mortality was very high in both arms of the study[16] and has been the subject of much debate.[17,18] The authors of the study[11] had stated that they would advise the study patients to withdraw selegiline therapy. Analysis of follow-up data[19] until the selegiline arm of the study was terminated (average 6.8 years) found an excess mortality of about 35%, a figure calculated[20] to be no longer significant. However, because of the premature termination of the study such results were considered[21] to be biased. Whether any excess in mortality is causally related to selegiline is still unclear. Some consider that changes in prescribing practice based on this study are not warranted.[17] Others[21] have made a cautious recommendation not to start combination treatment in patients with newly diagnosed Parkinson's disease but consider that there is little evidence to advise patients who have been using selegiline with levodopa for years without problem to change their treatment. An evaluation of mortality among patients taking antiparkinsonian drugs (using the UK General Practice Research Database) provided evidence against there being substantial excess mortality associated with the use of selegiline.[22] These results are supported by a systematic review[23] and meta-analyses[24,25] of randomised, double-blind studies which found no increase in mortality associated with selegiline treatment regardless of concurrent levodopa. Furthermore, increased mortality was not seen in patients in the original DATATOP trial[1] after an average follow-up time of 8.2 years. However, it was noted that the delay of disability observed in the early phase of selegiline therapy[1,7] was not associated with longer life during follow-up.[26] A recent systematic review[23] has also found no convincing evidence that selective monoamine oxidase type B inhibitors (selegiline and lazabemide) significantly delay disease progression in early Parkinson's disease and routine use is not recommended.

1. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; **321:** 1364–71.
2. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; **245:** 519–22.
3. Allain H, *et al.* Selegiline in de novo parkinsonian patients: the French selegiline multicenter trial (FSMT). *Acta Neurol Scand* 1991; **84** (suppl 136): 73–8.
4. Schulzer M, *et al.* The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992; **32:** 795–8.

5. Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; **57:** 217–20.
6. Brannan T, Yahr MD. Comparative study of selegiline plus -dopa–carbidopa versus -dopa–carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995; **37:** 95–8.
7. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; **39:** 29–36.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996; **39:** 37–45.
10. Olanow CW, *et al.* The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1996; **38:** 771–7.
11. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.
12. Myllylä VV, *et al.* Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995; **91:** 177–82.
13. Larsen JP, Boas J. Norwegian-Danish Study Group. The effects of early selegiline therapy on long-term treatment and parkinsonian disability: an interim analysis of a Norwegian-Danish 5-year study. *Mov Disord* 1997; **12:** 175–82.
14. Pålhagen S, *et al.* Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology* 2006; **66:** 1200–6.
15. Parkinson's Disease Research Group in the United Kingdom. Comparisons of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; **307:** 467–72.
16. Olanow CW, *et al.* Patients taking selegiline may have received more levodopa than necessary. *BMJ* 1996; **312:** 702–3.
17. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin Proc* 1996; **71:** 659–70.
18. Mizuno Y, Kondo T. Mortality associated with selegiline in Parkinson's disease: what do the available data mean? *Drug Safety* 1997; **16:** 289–94.
19. Ben-Shlomo Y, *et al.* Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998; **316:** 1191–6.
20. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998; **316:** 1183–4.
21. Breteler MMB. Selegiline, or the problem of early termination of clinical trials. *BMJ* 1998; **316:** 1182–3.
22. Thorogood M, *et al.* Mortality in people taking selegiline: observational study. *BMJ* 1998; **317:** 252–4.
23. Macleod AD, *et al.* Monoamine oxidase B inhibitors for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/02/06).
24. Olanow CW, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; **51:** 825–30.
25. Ives NJ, *et al.* Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; **329:** 593–6.
26. The Parkinson Study Group. Mortality in DATATOP: A multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; **43:** 318–25.

Smoking cessation. Selegiline has been investigated as an aid to smoking cessation (p.2354).

References.

1. George TP, *et al.* A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 2003; **53:** 136–43.
2. Biberman R, *et al.* A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction* 2003; **98:** 1403–7.

Preparations

BP 2008: Selegiline Oral Solution; Selegiline Tablets;
USP 31: Selegiline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

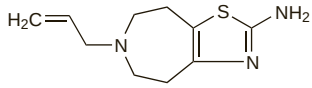
Arg.: Brintenal; Jumex; Kinabide†; Zelapar; ***Austral.:*** Eldepryl; Selgene; ***Austria:*** Amboneural; Cognitiv; Jumex; Regepar; Xilopar; ***Belg.:*** Eldepryl; ***Braz.:*** Deprilan; Elepril; Jumexil; Niar; Parkexin; ***Canad.:*** Eldepryl†; ***Chile:*** Selgina; ***Cz.:*** Apo-Seleg; Cognitiv; Jumex; Niar; Segalin†; Sepatrem†; ***Denm.:*** Eldepryl; ***Fin.:*** Eldepryl; ***Fr.:*** Deprenyl; Otrasel; ***Ger.:*** Amindan†; Antiparkin; Jutagilin; MAOtil†; Movergan; Selegam†; Selemerck; Selepark; Selgimed; Xilopar; ***Gr.:*** Cosmopril; Ermolax; Feliselin; Krautin; Legil; Procythol; Resostyl; ***Hong Kong:*** Julab; Jumex; Sefmex; Selegos; ***Hung.:*** Cognitiv; Jumex; Primulex†; ***India:*** Selerin; Selgin; ***Indon.:*** Jumex; ***Irl.:*** Eldepryl; ***Israel:*** Jumex; ***Ital.:*** Egibren; Jumex; Selecom; Seledat; Xilopar; ***Jpn:*** FP Tab; ***Malaysia:*** Ginex†; Jumex; Sefmex; Selegos†; ***Mex.:*** Niar; ***Neth.:*** Eldepryl; ***Norw.:*** Eldepryl; ***NZ:*** Eldepryl; Selgene†; ***Philipp.:*** Jumex; ***Pol.:*** Apo-Selin; Jumex; Parkinil†; Segan; Selerin; Selgin; Selgres; ***Port.:*** Jumex; Niponeurin; Xilopar; ***Rus.:*** Cognitiv (Когнитив); Segan (Сеган); Selegos (Селегос); ***S.Afr.:*** Eldepryl; Parkilyne; ***Singapore:*** Jumex; Selegos; ***Spain:*** Plurimen; ***Swed.:*** Eldepryl; ***Switz.:*** Jumexal; Selecim†; ***Thai.:*** Elegelin†; Julab; Jumex; Kinline†; Sefmex; Seline†; ***Turk.:*** Moverdin; Seldepar; ***UK:*** Eldepryl; Zelapar; ***USA:*** Atapryl; Carbex; Eldepryl; Emsam; Zelapar; ***Venez.:*** Jumex.

Talipexole Hydrochloride *(rINNM)*

Alefexole Hydrochloride; B-HT-920; Hidrocloruro de talipexol; Talipexole, Chlorhydrate de; Talipexoli Hydrochloridum. 6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.

Талипексола Гидрохлорид

$C_{10}H_{15}N_3S,2HCl$ = 282.2.
CAS — 101626-70-4 (talipexole); 36085-73-1 (talipexole hydrochloride).



(talipexole)

Profile

Talipexole hydrochloride is a dopamine D_2-agonist that is used in the management of parkinsonism (p.791) in usual oral doses of 1.2 to 3.6 mg daily, in divided doses. It has also been investigated in the treatment of schizophrenia.

Preparations

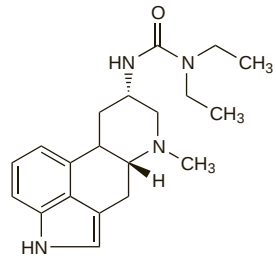
Proprietary Preparations (details are given in Part 3)
Jpn: Domin.

Terguride *(rINN)*

Tergurida; Terguridum. 1,1-Diethyl-3-(6-methylergolin-8α-yl) urea.

Тергурид

$C_{20}H_{28}N_4O$ = 340.5.
CAS — 37686-84-3.



Profile

Terguride, an ergot derivative, is a partial dopamine agonist with general properties similar to those of bromocriptine (p.798). It is used in the treatment of disorders related to hyperprolactinaemia (p.2079) in a usual oral dose of 500 micrograms twice daily. It is also being investigated in the management of parkinsonism.

◊ References.

1. Krause W, *et al.* Pharmacokinetics and endocrine effects of terguride in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 609–15.
2. Baronti F, *et al.* Partial dopamine agonist therapy of levodopa-induced dyskinesias. *Neurology* 1992; **42:** 1241–3.

Preparations

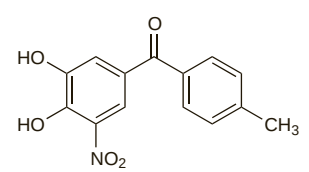
Proprietary Preparations (details are given in Part 3)
Cz.: Mysalfon†; ***Jpn:*** Teluron.

Tolcapone *(BAN, USAN, rINN)*

Ro-40-7592; Tolcapona; Tolcaponum; Tolkapon; Tolkaponi. 3,4-Dihydroxy-4′-methyl-5-nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl(4-methylphenyl)methanone.

Толкапон

$C_{14}H_{11}NO_5$ = 273.2.
CAS — 134308-13-7.
ATC — N04BX01.
ATC Vet — QN04BX01.



Pharmacopoeias. In *US.*

USP 31 (Tolcapone). A yellow, fine powder or fine powder with lumps. Insoluble in water and in *n*-hexane; Freely soluble in acetone and in tetrahydrofuran; sparingly soluble in chloroform and in dichloromethane; soluble in methyl alcohol and in ethyl acetate. Store in airtight containers at a temperature between 20° and 25°. Protect from light.

Adverse Effects

The most common adverse effects associated with tolcapone are diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, anorexia, dyskinesia, dystonia, dizziness, orthostatic hypotension, hallucinations, confusion, excessive dreaming, somnolence, headache, increased sweating, and sleep disorders. Diarrhoea may be severe enough for treatment to be stopped. Increases in liver enzyme values have occurred and hepatitis and hepatic failure, sometimes fatal, have been reported. Isolated cases of neuroleptic malignant syndrome have also been reported following dose reduction or stopping tolcapone; rhabdomyolysis may develop as a complication of the syndrome. Tolcapone and its metabolites can produce a yellow intensification in the colour of urine.

Effects on the liver. The UK CSM had noted[1] that, after a report[2] in September 1998 of fatal acute hepatic failure associated with tolcapone, the European Committee for Proprietary Medicinal Products (CPMP) had reviewed all reports of hepatic injury with tolcapone. There had been 10 reports of serious hepatic adverse reactions since tolcapone was marketed in October 1997, which included 7 reports of hepatitis, 3 of which had a fatal outcome. Serious hepatic reactions occurred unpredictably and their development was not always predicted by liver function monitoring. Consequently, in the EU, the marketing authorisation for tolcapone was suspended in November 1998. This suspension was lifted in April 2004 by the CPMP after further review.

In some countries such as the USA, tolcapone has always remained available albeit with restricted indications and strict monitoring requirements (see Precautions, below). Up to 2003, there had been no further reports of fatal hepatic failure following the introduction of these measures although the number of patients eligible to receive the drug has been reduced.[3]

1. CSM/MCA. Withdrawal of tolcapone (Tasmar). *Current Problems* 1999; **25:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. Assal F, *et al.* Tolcapone and fulminant hepatitis. *Lancet* 1998; **352:** 958.
3. Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Safety* 2003; **26:** 743–7.

Effects on the skin. For reference to the development of vitiligo in a patient following addition of tolcapone to levodopa/carbidopa treatment, see under Levodopa, p.806.

Precautions

Tolcapone should not be given to patients with hepatic impairment or raised liver enzyme values. Liver enzymes should be monitored:

- when starting treatment with tolcapone or on increasing the dose to 200 mg three times daily
- every 2 weeks during the first year of therapy
- every 4 weeks for a further 6 months
- every 8 weeks thereafter

Tolcapone should be stopped if liver enzyme levels exceed the upper limit of normal or if signs or symptoms suggestive of the onset of hepatic failure occur. Patients who have developed evidence of hepatic injury while receiving tolcapone should not be given the drug again.

Tolcapone should be used with caution in patients with severe renal impairment.

It is contra-indicated in patients with severe dyskinesia or with a history of neuroleptic malignant syndrome (NMS). It is also contra-indicated in patients with a history of nontraumatic rhabdomyolysis or symptoms of hyperpyrexia and confusion possibly related to NMS. Patients with phaeochromocytoma should not be given tolcapone.

Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Abrupt withdrawal or dose reduction of tolcapone should be monitored carefully because of the risk of developing symptoms resembling NMS.

The elderly. Confusion occurred in 3 elderly patients with severe Parkinson's disease after the addition of tolcapone to their antiparkinsonian therapy.[1] It was suggested that a starting dose of tolcapone 100 mg daily might be more suitable in frail patients with severe disease. It was noted[2] that a reduction in levodopa dosage is generally recommended when tolcapone is given to patients such as these, who were receiving 500 to 600 mg of levodopa daily.

1. Henry C, Wilson JA. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **351:** 1965–6.
2. Harper J, Vieira B. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **352:** 578.