

- Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005; **62**: 241–8.
- Rascol O, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 2005; **365**: 947–54.
- Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease: a review. *Expert Opin Pharmacother* 2005; **6**: 2061–75.
- Chen JJ, et al. Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol* 2005; **45**: 878–94.
- Siderowf A, Stern M. Clinical trials with rasagiline: evidence for short-term and long-term effects. *Neurology* 2006; **66** (suppl 4): S80–S88.
- Oldfield V, et al. Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007; **67**: 1725–47.

**Administration in hepatic impairment.** UK licensed product information for rasagiline advises caution when used in patients with mild hepatic impairment whereas US licensed information recommends that the dose be reduced to 500 micrograms daily. Rasagiline should not be used in those with moderate or severe impairment.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Elbrus; **Belg.:** Azilect; **Cz.:** Azilect; **Denm.:** Azilect; **Fin.:** Azilect; **Fr.:** Azilect; **Ger.:** Azilect; **Gr.:** Azilect; **Irl.:** Azilect; **Israel:** Azilect; **Neth.:** Azilect; **Norw.:** Azilect; **Pol.:** Azilect; **Port.:** Azilect; **Spain:** Azilect; **UK:** Azilect; **USA:** Azilect.

## Ropinirole Hydrochloride

(BANM, USAN, pINNMI)

Hydrocloruro de ropinirole; Ropinirole, Chlorhydrate de; Ropiniroli Hydrochloridum; SKF-101468 (ropinirole); SKF-0101468-A (ropinirole hydrochloride); 4-[2-(Dipropylamino)ethyl]-2-indolone hydrochloride.

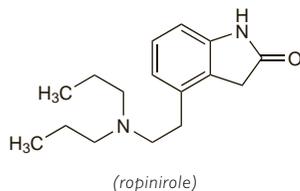
Ропинирола Гидрохлорида

C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O.HCl = 296.6.

CAS — 91374-21-9 (ropinirole); 91374-20-8 (ropinirole hydrochloride).

ATC — N04BC04.

ATC Vet — QN04BC04.



### Adverse Effects and Precautions

As for Bromocriptine, p.798. Licensed product information states that the pharmacokinetics of ropinirole have not been studied in patients with hepatic or severe renal impairment and therefore it should be used with caution, if at all, in such patients. No pharmacokinetic changes were noted in those with mild to moderate renal impairment.

In the treatment of restless legs syndrome, earlier onset of symptoms in the afternoon or evening (augmentation) and recurrence of symptoms in the early morning hours (rebound) have been reported with ropinirole.

#### Incidence of adverse effects. References.

- Etiman M, et al. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26**: 439–44.

**Effects on mental function.** For reports of daytime somnolence occurring in patients receiving dopamine agonists including ropinirole, see under Adverse Effects of Levodopa, p.805.

### Interactions

Since it is a dopamine agonist, ropinirole may share some of the pharmacological interactions of bromocriptine, p.800. In addition, high doses of oestrogens can increase plasma concentrations of ropinirole and dosage adjustments may be necessary if oestrogen therapy is started or withdrawn during treatment with ropinirole. Ropinirole is metabolised by the cytochrome P450 isoenzyme CYP1A2 and there is therefore the potential for interactions between ropinirole

and other drugs that are metabolised similarly or more particularly with inducers or inhibitors of this enzyme. Dosage adjustments may be necessary if therapy with such drugs is started or withdrawn during treatment with ropinirole.

### Pharmacokinetics

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have been achieved 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food. Bioavailability is reported to be about 50%. It is widely distributed throughout the body and plasma protein binding is low (10 to 40%).

Ropinirole is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP1A2, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported for ropinirole. It is thought to be distributed into breast milk on the basis of studies in rats.

#### References.

- Brefel C, et al. Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* 1998; **45**: 412–15.
- Hubble J, et al. Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. *J Clin Pharmacol* 2000; **40**: 641–6.
- Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* 2000; **39**: 243–54.

### Uses and Administration

Ropinirole is a non-ergot dopamine D<sub>2</sub>-agonist with similar actions to those of bromocriptine (p.800), but in contrast to bromocriptine it also has agonist properties at D<sub>3</sub> receptors. It is used similarly in the management of Parkinson's disease, either alone or as an adjunct to reduce 'on-off' fluctuations in levodopa response. Ropinirole is also used for the treatment of moderate to severe idiopathic restless legs syndrome. It is given by mouth as the hydrochloride; doses are expressed in terms of the base. Ropinirole hydrochloride 1.14 mg is equivalent to about 1 mg of ropinirole.

In the treatment of Parkinson's disease, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over the period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets.

Ropinirole is also given as a single daily dose, 1 to 3 hours before bedtime, in the treatment of restless legs syndrome. The initial dose of ropinirole is 250 micrograms daily for 2 days; if tolerated, the dose is then increased to 500 micrograms daily for the rest of the first week. Subsequent increases may be made in weekly steps of 500 micrograms until a dose of 3 mg daily is reached; if necessary, the dose may then be increased after 1 further week to a maximum of 4 mg daily.

In the UK, it has been recommended that treatment should be re-assessed 3 months after starting therapy. For this indication, ropinirole may be withdrawn without gradual tapering of the dose.

If treatment with ropinirole is interrupted for more than a few days it should be restarted at the low initial dose and increased gradually as required.

#### Reviews.

- Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; **49** (suppl 1): S58–S62.

**Parkinsonism.** Dopamine agonists such as ropinirole may be used to begin treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease.

#### References.

- Rascol O, et al. A placebo-controlled study of ropinirole a new D<sub>2</sub> agonist, in the treatment of motor fluctuations of -DOPA-treated parkinsonian patients. *Adv Neurol* 1996; **69**: 531–4.
- Adler CH, et al. The Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49**: 393–9.
- Rascol O, et al. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13**: 39–45.
- Korczyn AD, et al. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53**: 364–70.
- Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. *Drugs* 2000; **60**: 115–37.
- Clarke CE, Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
- Clarke CE, Deane KHO. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
- Whone AL, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54**: 93–101.
- Pahwa R, et al. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007; **68**: 1108–15.

**Restless legs syndrome.** The aetiology of restless legs syndrome (RLS)—see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Ropinirole is licensed for the treatment of moderate to severe RLS in some countries.

#### References.

- Trenkwalder C, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004; **75**: 92–7.
- Cheer SM, et al. Ropinirole for the treatment of restless legs syndrome. *CNS Drugs* 2004; **18**: 747–54.
- Walters AS, et al. Ropinirole is effective in the treatment of restless legs syndrome—TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004; **19**: 1414–23.
- Bogan RK, et al. TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81**: 17–27.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Requip; **Austral.:** Repreve; **Austria:** Requip; **Belg.:** Requip; **Canad.:** Requip; **Chile:** Requip; **Cz.:** Adartrel; Requip; **Denm.:** Requip; **Fin.:** Requip; **Fr.:** Adartrel; Requip; **Ger.:** Requip; **Gr.:** Adartrel; Requip; **Hong Kong:** Requip; **Hung.:** Requip; **Irl.:** Requip; **Israel:** Requip; **Ital.:** Requip; **Malaysia:** Requip; **Neth.:** Requip; **Norw.:** Requip; **NZ:** Requip; **Pol.:** Requip; **Port.:** Requip; **S.Afr.:** Requip; **Singapore:** Requip; **Spain:** Requip; **Swed.:** Requip; **Switz.:** Adartrel; Requip; **Turk.:** Requip; **UK:** Adartrel; Requip; **USA:** Requip.

## Rotigotine (USAN, rINN)

N-0923; Rotigotina; Rotigotinum; SPM-962. (–)-(S)-5,6,7,8-Tetrahydro-6-(propyl[2-(2-thienyl)ethyl]amino)-1-naphthol.

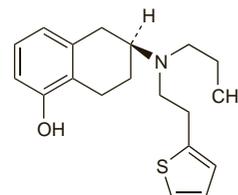
РОТИГОТИН

C<sub>19</sub>H<sub>25</sub>NOS = 315.5.

CAS — 99755-59-6 (rotigotine); 125572-93-2 (rotigotine hydrochloride).

ATC — N04BC09.

ATC Vet — QN04BC09.



### 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<sub>2</sub>-agonist with similar actions to those of bromocriptine (p.798), but in contrast to bromocriptine (a dopamine D<sub>2</sub>-agonist) it also has agonist properties at D<sub>1</sub> and D<sub>3</sub> 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, Leuzzi 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; Selegilinihidroklorid; Selegilin-Hidroklorür; Selegilin hydrochlorid; Sélegiline, chlorhydrate de; Selegilinihydroklorid; Selegilini hydrochloridum; Selegilino hydrochloridas; Szelegilin-hidroklorid. (-)-(R)-N,α-Dimethyl-N-(prop-2-ynyl)phenethylamine hydrochloride; (R)-Methyl(α-methylphenethyl)prop-2-ynylamine hydrochloride.

Селегилина Гидрохлорид

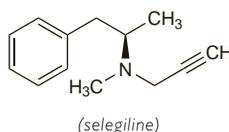
C<sub>13</sub>H<sub>17</sub>N, HCl = 223.7.

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

ATC — N04BD01.

ATC Vet — QN04BD01.

The symbol † denotes a preparation no longer actively marketed



**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.<sup>1</sup> 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<sup>1</sup> of the autonomic effects of selegiline as a potential cause of the unexpected mortality observed in a study<sup>2</sup> 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<sup>2</sup> or paroxetine<sup>2</sup> (apparently without any problems) there have been reports of reactions<sup>3-5</sup> such as shivering and sweating, hypertension, hyperactivity, and ataxia occurring when selegiline and fluoxetine have been used together. The FDA noted<sup>6</sup> 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*.<sup>6</sup> 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<sup>7</sup> 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.<sup>8</sup> 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*.<sup>1</sup>

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

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)