NEW DRUGS

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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Rasagiline mesilate

Approved indication: Parkinson's disease
Azilect (Lundbeck)
1 mg tablets
Australian Medicines Handbook section 16.2.3

When Parkinson's disease requires drug treatment, the patient is usually prescribed a drug containing levodopa or a dopamine agonist. Another treatment option is an inhibitor of monoamine oxidase type B. Blocking this enzyme increases the concentration of dopamine in the brain. Selegiline is a monoamine oxidase type B inhibitor which has been available for several years. It is now joined by rasagiline which can be used as monotherapy or with levodopa.

Rasagiline is a once-daily treatment. The tablet can be taken with or without food. Although the drug appears to be selective for monoamine oxidase type B at recommended doses, there is a potential for interactions with foods, such as aged cheeses, which contain high concentrations of tyramine. Rasagiline is metabolised by the liver and liver impairment is a contraindication. The metabolites of rasagiline are mainly excreted in the urine. Unlike selegiline, rasagiline is not converted into amphetamine metabolites.

The metabolism of rasagiline involves cytochrome P450 1A2. Rasagiline should not be given with ciprofloxacin or other inhibitors of this enzyme. Fluvoxamine should be avoided as it is also metabolised by cytochrome P450 1A2. A serotonin syndrome may also result if rasagiline is used with antidepressant drugs. Monoamine oxidase inhibitors and St John's wort are contraindicated. Other contraindicated medicines include pethidine, tramadol and methadone.

Rasagiline was compared to placebo in 404 patients with early Parkinson's disease. The main outcome of the study was the change in the 176-point Unified Parkinson's Disease Rating Scale. At the start of the study the patients had mean scores of 24–25. After 26 weeks, impairment had increased by 0.1 with rasagiline 1 mg, 0.7 with rasagiline 2 mg, and 3.9 with placebo.[1] The patients in the placebo group were then switched to rasagiline 2 mg. One year after the trial began, the increases in the scores were 3.01 with 1 mg rasagiline, 1.97 with 2 mg rasagiline, and 4.17 in the patients who switched to rasagiline from placebo.[2]

The possible advantages of starting rasagiline early in the course of the disease were studied in a trial of 1176 previously untreated patients. These patients were randomised to start rasagiline at once or after 36 weeks. A total of 588 patients were given the 1 mg daily dose recommended in Australia. From mean baselines of 20–21 points, the rate of change in their scores on the Unified Parkinson's Disease Rating Scale showed a slower rate of deterioration when treatment was started sooner. After 72 weeks the score had changed by 2.82 points with early treatment and by 4.5 points with delayed treatment. However, early or delayed treatment did not have a significantly different effect on the total scores of the other patients who were given 2 mg.[3]

Patients who have been treated with levodopa eventually develop motor complications. These fluctuations adversely affect the patient's quality of life and can be difficult to control. Rasagiline has therefore been studied as an adjunct to levodopa.

Patients (n=472) with at least 2.5 hours of 'off time' each day were randomised to add rasagiline or a placebo to their levodopa treatment. After 26 weeks, off time was reduced by 1.85 hours with rasagiline 1 mg and by 1.41 hours with 0.5 mg. Off time was reduced by 0.91 hours in the placebo group.[4]

Entacapone was included in another placebo-controlled trial of rasagiline involving 687 patients who were having motor fluctuations for at least one hour every day while taking levodopa. After 18 weeks the average reduction in off time was 1.18 hours with rasagiline 1 mg, 1.2 hours with entacapone and 0.4 hours with placebo.[5]

The dopaminergic actions of rasagiline are associated with adverse reactions such as hallucinations and postural hypotension. Common adverse effects include headache, arthralgia, dyspepsia and dizziness. In one of the adjunctive studies, anorexia, vomiting and weight loss were more frequent with rasagiline 1 mg than with placebo. Although 'on time' increased, 32% of the increase included troublesome dyskinesias.[4]

The Therapeutic Goods Administration originally rejected the application to register rasagiline in Australia because of an apparent increase in the risk of melanoma. However, it is uncertain that the drug was responsible. As a precaution, patients should have periodic checks for skin cancer.

Although rasagiline has statistically significant effects as monotherapy its clinical effectiveness seems uncertain. The Unified Parkinson's Disease Rating Scale has a range of 176 points, so small changes may not be clinically significant. Any benefit of early treatment was lost if a higher dose of rasagiline was used.[3] Early treatment may not significantly delay the need for levodopa.[1]

While rasagiline can be added to treatment with levodopa, it is unclear if it is more effective than selegiline or other adjunctive therapies. The trial which studied rasagiline and entacapone did not have the statistical power to detect any differences between them.[5]

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The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)