

NEW DRUG EVALUATION

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RASAGILINE

Rasagiline is a selective MAO-B inhibitor licensed for the treatment of Parkinson's disease. As monotherapy for early disease, rasagiline reduces symptoms and improves functioning compared with placebo. As adjunctive therapy for patients with more advanced disease experiencing motor fluctuations with levodopa, it reduces off time by an average of half to one hour per day and increases on time. Dopaminergic adverse effects are common when it is given with levodopa. The long-term efficacy and safety of rasagiline and its relative efficacy compared with other drugs for Parkinson's disease have not been examined and its role in treatment cannot be currently defined

What is it?

Rasagiline (Azilect[®], Teva) like selegiline, is a selective inhibitor of monoamine oxidase B (MAO-B). It is licensed, at a dose of 1 mg/day, for the treatment of Parkinson's disease (PD) as monotherapy in patients with early disease or as an adjunct to levodopa therapy in patients with end of dose motor fluctuations¹. No dose titration is required and a dose reduction is not recommended for older patients.

How effective is it?

Rasagiline has been evaluated as monotherapy² and as an adjunct to levodopa^{3,4} in three large double-blind, placebo-controlled trials. No trial comparing it with selegiline or other drugs for Parkinson's disease has been published.

In the TEMPO study,² 404 patients with early Parkinson's disease (mean age approximately 60, mean duration of disease approximately one year) who did not need dopaminergic therapy were randomised to treatment with rasagiline 1 or 2 mg/day or placebo. After 6 months, both doses of rasagiline were associated with statistically significant reductions in the Unified Parkinson's Disease Rating Scale (UPDRS) score. Response rates (defined as a worsening of less than 3 units of the UPDRS score) were 66% and 67% with rasagiline 1 and 2 mg/day and 49% with placebo. The proportions of patients who needed levodopa treatment after 6 months were 11.2%, 16.7% and 16.7% respectively. Rasagiline was also associated with significant improvements in quality of life scores compared with placebo.

In the second arm of the study,⁵ patients who had been assigned to rasagiline continued treatment and placebo recipients (n=132) were treated with rasagiline 2 mg/day (licensed dose is 1 mg daily). After a further 6 months, there was significantly less functional decline in patients who had been taking rasagiline for a total of 12 months compared with those who had started treatment 6 months later. This difference, which was approximately half as great as that between rasagiline and placebo in the original study, was interpreted as evidence of a disease-modifying effect but longer term blinded studies would be required to confirm this. Both active treatment groups showed significant improvements in quality of life scores compared with the placebo group.

Rasagiline has also been evaluated as adjunctive therapy to levodopa in older patients with more advanced Parkinson's disease and motor fluctuations (mean disease duration 9 - 10 years) in two trials.^{3,4} The primary endpoint in both was the change in off time (poor or absent motor function). The dose of levodopa could be adjusted only during the first 6 weeks in each trial; other treatments for Parkinson's disease were allowed.

In the PRESTO trial,³ 472 patients experiencing off time for at least 2.5 hours/day (mean 6 hours) were randomised to placebo or rasagiline 0.5 or 1 mg/day in addition to established levodopa therapy (mean dose at baseline 750 - 821 mg/day). After 6 weeks, mean total daily off time was significantly reduced at a dose of 1 mg/day compared with placebo. After 6 months, rasagiline 0.5 and 1 mg/day were associated with reductions in off time of 0.49 and 0.94 hours respectively compared with placebo. Total daily on time (relatively good overall function) was increased from 9 - 10 hours by 0.51 hours at 0.5 mg/day and by 0.78 hours at 1 mg/day. However, approximately 30% of the gain in on time at the higher dose was associated with dyskinesias. The dose of levodopa was reduced by a mean of 12, 32 and 36 mg/day with placebo, rasagiline 0.5 mg/day and 1 mg/day respectively. Rasagiline did not significantly improve overall quality of life.

In the LARGO trial,⁴ 687 patients experiencing motor fluctuations for at least one hour during off time were randomised to 18 weeks treatment with rasagiline 1 mg/day, the catecholamine-O-methyl transferase (COMT) inhibitor entacapone (200 mg with each dose of levodopa), or placebo; rasagiline and entacapone were not directly compared. Mean daily off time at baseline was approximately 5.6 hours. In 658 patients for whom data were analysed, mean total daily off time was significantly reduced by rasagiline (by 0.78 hour) and entacapone (0.80 hour) compared with placebo. The response rate (defined as at least a one-hour decrease in off time) was 51% with rasagiline, 45% with entacapone and 32% with placebo. The mean dose of levodopa at baseline was 697 - 722 mg/day; this was reduced by a mean of 24 mg/day with rasagiline and 19 mg/day with entacapone but increased by 5 mg/day with placebo. Response rates were not affected by age under or over 70, or by concurrent treatment with a dopamine agonist. Quality of life was not evaluated.

How safe is it?

In blinded trials lasting up to 6 months, the overall frequency of adverse events was similar between rasagiline and entacapone.²⁻⁴ Compared with placebo, rasagiline monotherapy (1 mg/day) was associated with a higher incidence of asthenia (10.9% vs. 4.5%)². As adjunctive therapy compared with placebo rasagiline 1 mg/day was associated with a higher incidence of weight loss (9.4% vs. 2.5%), vomiting (6.7% vs. 1.3%) and anorexia (5.4% vs. 0.6%) in the PRESTO trial³ Postural hypotension was reported in the LARGO trial (2% with rasagiline 1 mg/day vs. 0% with placebo).⁴

What other options are there?

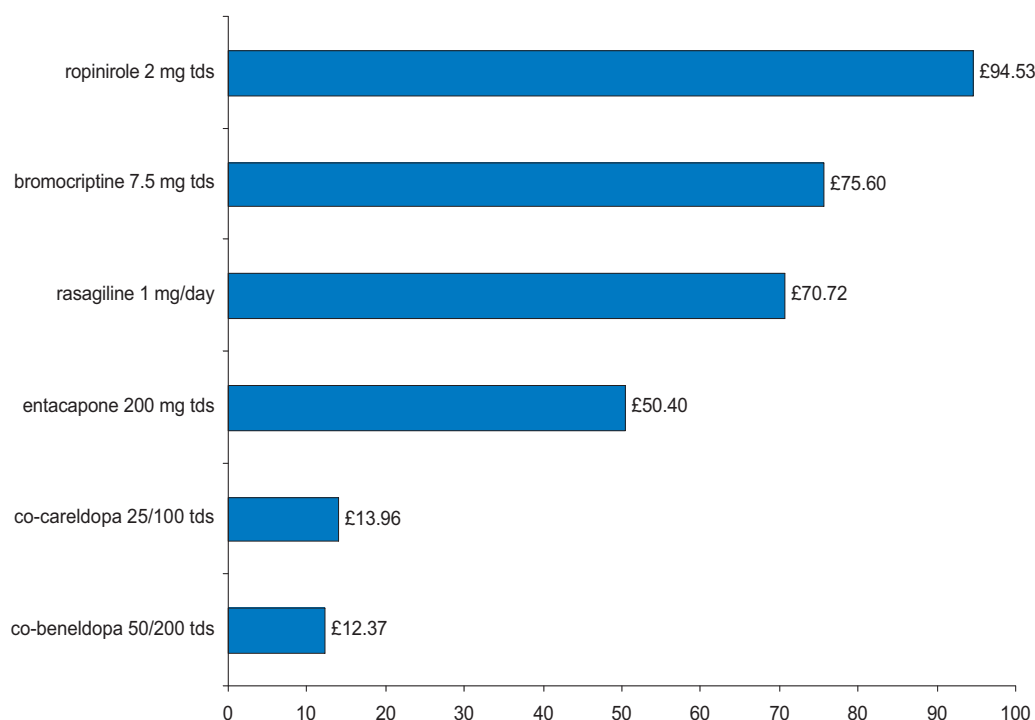
A dopamine agonist or levodopa is preferred to selegiline as monotherapy for early Parkinson's disease,⁶ although the question of which to use first is unresolved. Adjunctive therapies with levodopa include dopamine agonists, selegiline and the COMT inhibitors entacapone and (when entacapone is indicated but has failed) tolcapone.

When should rasagiline be used?

The simple dose regimen and lack of dose titration with rasagiline may aid compliance but its efficacy and long-term safety compared with alternative agents is unknown. Its role cannot be defined until comparative trials with more established treatments have been published.

How much does it cost?

Cost for 28 days treatment (prices from MIMS November 2005/Drug Tariff November 2005)



NB Doses shown are for general comparison only and do not imply therapeutic equivalence.

REFERENCES

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KEY RCT - randomised controlled trial, R - review

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