

## Rasagiline

Concise evaluated information to support the managed entry of new medicines in the NHS

### Summary

- Rasagiline is a selective, irreversible monoamine-oxidase B inhibitor licensed for the treatment of idiopathic Parkinson's disease (PD) as either mono- or combination therapy. It is given at a dose of 1mg daily without the need for dose titration.
- In the TEMPO study, conducted in patients with early PD, rasagiline monotherapy was more effective than placebo as measured by changes in the Unified Parkinson's Disease Rating Scale over a 26-week period.
- In patients with more advanced PD on optimal doses of levodopa, the 6 month PRESTO study found the addition of rasagiline to be more effective than placebo in decreasing off-time and increasing on-time without dyskinesia.
- In a similar population, the 18-week LARGO study compared rasagiline and entacapone with placebo when added to a stable PD drug regimen. Rasagiline 1mg daily reduced off-time and improved motor control compared with placebo and to a similar magnitude as entacapone, although the study was not powered for the latter comparison.
- Adverse events seen with rasagiline did not differ greatly from those seen with placebo during the trials.
- Treatment with rasagiline should be initiated by a physician specialising in the treatment of PD.

### Introduction

Rasagiline was launched in June 2005 for the treatment of idiopathic Parkinson's disease (PD), at a dose of 1mg daily. It can be used as monotherapy or as adjunct therapy to levodopa in patients with end-of-dose fluctuations.

Rasagiline is a selective, irreversible inhibitor of monoamine-oxidase B (MAO-B), an enzyme found in the neurons of the hypothalamus responsible for the metabolism of dopamine. Inhibition of MAO-B can help conserve depleted dopamine supply, which is a feature of PD, and delay the need for exogenous levodopa therapy, or allow for the use of lower doses in patients with advanced disease. Unlike selegiline, also an MAO-B inhibitor, rasagiline is not converted into amphetamine metabolites.

### Evidence

Three pivotal trials were submitted to the EMEA for marketing authorisation: TEMPO, PRESTO and LARGO.

TEMPO<sup>1,2</sup> consisted of two 26-week phases. The first was a randomised, double-blind, placebo controlled phase where patients were given either placebo (n=138) or rasagiline 1mg (n=134) or 2mg (n=132) per day. During the second 26-week phase patients either continued with rasagiline or, if they had originally been randomised to placebo, treatment with rasagiline 2mg/day was initiated. The delayed-start design was intended to separate out an immediate symptomatic effect from an effect on disease progression.

Patients with early, untreated Parkinson's disease who had not developed sufficient disability to require dopaminergic therapy were eligible for entry. Concomitant treatment with anticholinergics was allowed. The primary efficacy measure was the change in the total Unified Parkinson's Disease

**Brand Name, (Manufacturer):** Azilect [Lundbeck/Teva]

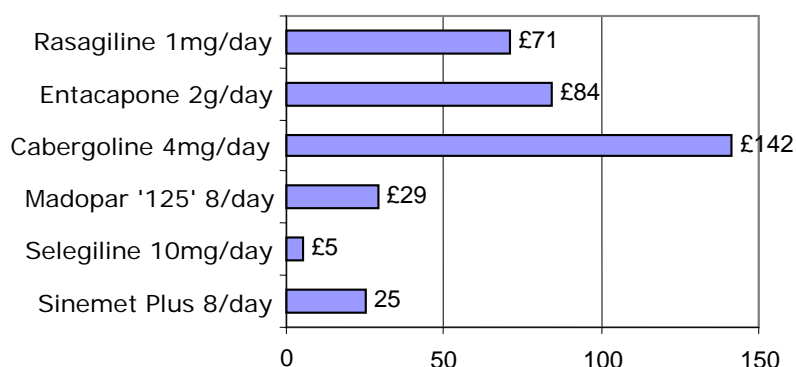
**BNF Therapeutic Class:** 4.9.1 Dopaminergic drugs used in parkinsonism

**Licensed Indications:** The treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

**Dosage and Administration:** 1mg/day with or without levodopa

**Marketed:** June 2005

**Cost Comparisons:** Costs for 28 days treatment.



N.B. Doses shown for general comparison and do not imply therapeutic equivalence.

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Rating Scale (UPDRS) from baseline to week 52.

Over the initial 26-week period the use of rasagiline 1mg and 2mg daily resulted in better overall UPDRS performance than placebo ( $p < 0.001$ ) and no clinical advantage of using the higher dose was noted. After 52 weeks, the continuous use of rasagiline resulted in smaller increases in the UPDRS compared with placebo/delayed 2mg rasagiline. Changes from baseline were  $1.97 \pm 7.49$  (2mg),  $3.01 \pm 8.26$  (1mg) and  $4.17 \pm 8.83$  (placebo/2mg), indicating greater functional decline in subjects whose treatment was delayed for 6-months. It is postulated that this represents a possible neuroprotective effect of rasagiline.

The PRESTO<sup>3</sup> study was a 6-month randomised, double-blind, placebo-controlled, parallel-group study comparing rasagiline 0.5mg/day ( $n=164$ ), 1mg/day ( $n=149$ ) or matching placebo ( $n=159$ ). Patients had idiopathic PD with at least 2.5 hours of off-time (a state of poor or absent motor function) a day. They had optimised on stable levodopa doses given at least 3 times a day for at least 2 weeks before screening. Concomitant treatment with dopamine agonists, amantadine, anticholinergics and entacapone was allowed. The primary efficacy measure was the mean total daily off-time.

Rasagiline use was associated with decreased off-time and increases in daily on-time without troublesome dyskinesias. The difference in off-time between rasagiline 0.5mg and placebo was  $-0.49$  hours [95% CI  $-0.91, -0.08$ ,  $p=0.02$ ] and between rasagiline 1mg and placebo,  $-0.94$  hours [ $-1.36, -0.51$ ,  $p < 0.00$ ]. Neurological function was improved during both on- and off-time and benefits were seen as early as six weeks after starting therapy. The greatest neurological improvements were in the 1mg/day group, but differences between the 0.5mg and 1mg groups were not statistically significant.

The LARGO<sup>4</sup> study was an 18-week, randomised, double-blind, placebo-controlled, double-dummy, parallel-

group study in patients with advanced idiopathic PD on at least three, and not more than eight doses, of levodopa a day. Patients were randomised to either rasagiline 1mg/day ( $n=231$ ), entacapone 200mg with every levodopa dose ( $n=227$ ) or placebo ( $n=229$ ). Concomitant stable adjunctive treatment for PD was continued.

Both rasagiline and entacapone reduced the primary outcome, mean daily off-time, compared with placebo (rasagiline treatment effect 0-78 hours, 95% CI 0-39, 1-18,  $p=0.0001$ ; entacapone treatment effect 0-80 hours, 0-41, 1-20,  $p < 0.0001$ ). On-time without troublesome dyskinesias increased with both drugs by 0-82 hours more than with placebo (95% CI 0-36, 1-27,  $p=0.0005$ ). Although this trial was not designed to directly compare rasagiline with entacapone, the results show their clinical effects to be similar. There were no differences in withdrawal rate between the three groups and benefits were independent of age ( $< 70$  vs  $\geq 70$  years) and whether or not patients were receiving a dopamine agonist.

## Safety

In these three studies the frequency of adverse events was not significantly different between treatment groups.

Further details of adverse effects can be found in the Azilect SPC via <http://emc.medicines.org.uk/>.

MAO inhibitors are known to be involved in a number of drug interactions. Rasagiline should not be used with other MAO inhibitors, pethidine, sympathomimetic agents such as those used in decongestants, dextromethorphan and the antidepressants: fluoxetine and fluvoxamine.

## Place in Therapy

Parkinson's disease affects about 120,000 people in the UK (approximately 200 per 100,000 population). Treatment of new

patients is often started with dopamine agonists, which are also used with levodopa in more advanced disease. Other drugs used as adjunctive therapy with levodopa include entacapone, selegiline, amantadine and apomorphine.

Rasagiline has not been compared with dopamine agonists for the initial treatment of PD, nor is there any comparative trial data to inform the decision about which class of adjuvant therapy is most effective and safe. The ongoing PD MED trial is randomising patients with motor complications between any dopamine agonist, any MAOI-B inhibitor and any inhibitor of catechol-O-methyl transferase and may provide the evidence on which to base a decision on adjunctive therapy.

Many of the treatments for PD have initially complicated dosing regimes, requiring dose titration. Rasagiline has a simple regimen of 1mg daily without the need for dose titration, making it an attractive choice for patients, carers and prescribers.

The proposal that rasagiline has a neuroprotective effect remains speculative and should not influence prescribing decisions. Treatment with rasagiline should be initiated by a physician specialising in the treatment of PD.

## Key Papers

1. Siderowf et al. Archives of Neurology 2002; 59 (12): 1937-1943.
2. Siderowf et al. Archives of Neurology 2004; 61 (4): 561-566.
3. Schwid et al. Archives of Neurology 2005; 62 (2): 241-248.
4. Rascol et al. Lancet 1005; 365: 947-954.

The full LNDG document can be found on the [NeLM](#).

## Risk Management Issues:

None identified.

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