

**rasagiline 1mg tablet (Azilect<sup>®</sup>)**

**Lundbeck / Teva Pharmaceuticals**

**No. 243/06**

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**rasagiline (Azilect<sup>®</sup>)** is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa).

Rasagiline provides symptomatic improvement for patients with early Parkinson's disease. However, there are no comparative data with the other monoamine-oxidase-B inhibitor, which is less expensive. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Rasagiline 1mg tablet  
(Azilect®)**

**Indication**

Treatment of idiopathic Parkinson's disease as monotherapy (without levodopa).

**Dosing information**

1mg once daily

**UK launch date**

4 July 2005

**Comparator medications**

One other monoamine-oxidase-B (MAO-B) inhibitor, selegiline, is licensed for use as monotherapy in the UK for the treatment of Parkinson's disease (PD). Other drugs licensed for this indication include levodopa plus a dopa decarboxylase inhibitor (co-beneldopa and co-careldopa) and the dopamine receptor agonists (bromocriptine, pergolide, pramipexole and ropinirole).

**Cost of relevant comparators**

| Class                                      | Drug              | Daily dose range**           | Annual cost (£)* |
|--|-------------------|------------------------------|------------------|
| <b>MAO-B inhibitor</b>                     | <b>Rasagiline</b> | <b>1mg daily</b>             | <b>922</b>       |
|  | Selegiline        | 10mg daily                   | 104              |
| Levodopa plus dopa decarboxylase inhibitor | Co-beneldopa SR   | 400-800mg daily <sup>+</sup> | 233-466          |
|  | Co-careldopa      | 400-800mg daily <sup>+</sup> | 163-232          |
|  | Co-careldopa SR   | 400-800mg daily <sup>+</sup> | 147-294          |
|  | Co-beneldopa      | 400-800mg daily <sup>+</sup> | 126-215          |
| Dopamine agonist                           |                   |                              |                  |
|  | Ropinirole        | 3-9mg daily                  | 616-1848         |
|  | Pergolide         | 2-2.5mg daily                | 575-806          |
|  | Pramipexole       | 0.264-2.64mg daily           | 338-2825         |
|  | Bromocriptine     | 10-40mg daily                | 272-1088         |

\*costs from eVadis accessed on 28<sup>th</sup> November 2005; \*\* based on usual dose ranges – these do not indicate therapeutic equivalence; + expressed as levodopa dose; MAO-B monoamine oxidase-B.

## Summary of evidence on comparative efficacy

Rasagiline is an irreversible inhibitor of the MAO-B enzyme. One effect of this enzyme inhibition is an increase in extracellular dopamine levels in the striatum, with subsequently increased dopaminergic activity. This is thought to be the likely mechanism of action of rasagiline in PD.

A double-blind trial recruited 404 adults aged >35 years with idiopathic PD, defined by the presence of two cardinal signs (resting tremor, bradykinesia or rigidity) who had a disease severity score of  $\leq 3$  on the modified Hoehn and Yahr scale. They were randomised to placebo or rasagiline (1mg or 2mg) once daily for 26 weeks and continued any anticholinergic drugs for PD at stable doses throughout the study. All other medicines for PD had been discontinued. The primary outcome was mean change from baseline to week 26 in total unified PD rating scale (total UPDRS) score, which ranges from 0-124, with higher scores indicating more severe disease. This was compared between each rasagiline group and the placebo group using analysis of covariance (ANCOVA) models, which included baseline values as a covariate. Mean change from baseline to week 26 in total UPDRS score was significantly lower with both rasagiline 1mg and 2mg compared to placebo, with mean (95% confidence intervals (CI)) treatment effects over placebo of -4.20 (-5.66, -2.73) and -3.56 (-5.04, -2.08), respectively. In similar analyses, mean change from baseline to week 26 in UPDRS subscales of motor function (range 0-56), and activities of daily living (ADL, range 0-52) were significantly lower in each rasagiline group compared to placebo, with mean (95% CI) treatment effects over placebo with rasagiline 1mg of -2.71 (-3.87, -1.55) and -1.04 (-1.60, -0.48) for the respective outcomes. Total PD quality of life (PDQUALIF) scores (range 0-100) significantly improved from baseline to week 26, with a mean (95% CI) treatment effect for rasagiline 1mg over placebo of -2.91 (-5.19, -0.64). Exploratory analyses suggest that benefits occurred primarily in the self-image/sexuality subscale, with borderline effects in the social role subscale.

The second 6-month double-blind phase of this study included 380 patients who completed 26 weeks in the first part of the study or required additional dopaminergic therapy before 26 weeks and entered the active-controlled phase at this point. In this phase patients who had received rasagiline in the preceding phase continued on the same doses and patients who had received placebo received rasagiline 2mg daily. The latter group was termed the delayed-treatment group. The primary outcome, mean change from baseline to week 52 in total UPDRS, was compared between the delayed-treatment group and both of the other groups via ANCOVA, which included baseline values as a covariate. The mean change from baseline to week 52 in total UPDRS was of borderline significance in the rasagiline 1mg group compared to the delayed-treatment group, with mean (95% CI) treatment effect over this group of -1.82 (-3.64, 0.01),  $p=0.05$ . The mean change from baseline to week 52 in total UPDRS was significantly lower in the rasagiline 2mg group compared with the delayed-treatment group, with mean (95% CI) treatment effect over this group of -2.29 (-4.11, -0.48). There were no significant differences between either of the rasagiline 1mg or 2mg groups and the delayed-treatment group in change from baseline to week 52 in UPDRS motor, ADL or mental subscales, except for ADL subscale in the rasagiline 2mg group, which was significantly lower than the delayed-treatment group, with a mean (95% CI) treatment effect over this group of -0.96 (-1.64, -0.29).

An open-label extension to this study included 306 patients who were treated with rasagiline for up to 6.5 years, with additional therapy for PD as required. In analyses of all 404 patients, which pooled data for the groups receiving rasagiline from the start of the placebo-controlled phase, termed the early-treatment group, there were no significant differences between this group and the delayed-treatment group in median time to initiation of levodopa or dopamine

agonist (1.5 and 1.8 years in the respective groups) or proportion of patients given either of these drugs (66% and 70% respectively). There were also no significant differences between the groups in median time to levodopa (4.1 and 4.2 years respectively) or the proportion of patients given levodopa (46% and 44% respectively).

### **Summary of evidence on comparative safety**

In double-blind placebo-controlled clinical trials of rasagiline adverse effects were non-specific at doses up to 1mg daily. Analysis of safety data from two 6-month double-blind, placebo-controlled trials, one described previously and one in late PD, was conducted in subgroups aged  $\geq 70$  years and  $< 70$  years. Total adverse effects, total serious adverse effects and symptomatic postural hypotension were not significantly affected by treatment group or age.

### **Summary of clinical effectiveness issues**

The European Medicines Agency noted that the effect of rasagiline as monotherapy in early PD (a 4-point improvement in total UPDRS score over placebo) is modest, compared for example to historical data for other drugs, in particular dopamine agonists, but appears at least comparable to selegiline based on historical data. No trials directly compare rasagiline with selegiline, the other MAO-B inhibitor marketed in the UK, or with dopamine agonists in early PD. Therefore, efficacy and safety of rasagiline relative to these drugs is uncertain.

The delayed-start design of the study in early PD was intended to investigate possible disease-modifying or neuroprotective effects of rasagiline, which might be indicated by constantly maintained significant differences in UPDRS scores between the delayed- and early-treatment groups. Although a significant difference was found between delayed-treatment and rasagiline 2mg early-treatment group at one year, the difference compared to rasagiline 1mg early-treatment group was of borderline significance. Also the duration of this active-controlled phase may be insufficient to observe UPDRS score merge, as would occur if rasagiline exhibited only symptomatic effects. In longer follow-up during the open-label extension phase, median times to initiation of additional therapy and proportions of patients requiring this appear similar in both groups, suggesting no clinically significant differences in disease management. There is no convincing evidence that rasagiline exhibits disease-modifying or neuroprotective effects.

### **Summary of comparative health economic evidence**

The manufacturer presents a Markov model implemented through a probabilistic sensitivity analysis. This models patients within 6-monthly cycles over 5 years within 2 arms:

- Starting first-line rasagiline. These patients may progress directly to levodopa, or to an approximately 50:50 split between the second-line dopamine agonists, ropinirole and pramipexole. Those on the second-line dopamine agonists may then progress to levodopa.
- Starting on a similar 50:50 split between the first-line dopamine agonists, ropinirole and pramipexole. These patients then progress to levodopa.

Treatments are differentiated by their direct drug costs and the probabilities of moving between treatments within the model. The transition probabilities for moving from rasagiline to either ropinirole, pramipexole or levodopa are taken from the trial in early PD described previously. Other transition probabilities are interpolated from 5- or 4-year data within the literature, though the comparability of these figures is not immediately clear. The model outputs are cost and time to use of levodopa. The manufacturer translates this time to use of

levodopa into quality adjusted life years through the application of a common quality of life value. This appears to implicitly assume that extending time to use of levodopa results in an equivalent survival gain which is questionable.

Second-line treatment with a dopamine agonist has been assumed to have the same effectiveness as first-line treatment, which may bias the analysis towards rasagiline. The assumption that, after a switch from rasagiline, patients had equal chance of receiving ropinirole or pramipexole could be to the disadvantage of ropinirole in terms of both cost and effectiveness and, by implication, to the advantage of rasagiline.

The assumption in the model that by the end of year 5 only 31% of patients in the group starting on rasagiline, will have progressed to levodopa use versus 72% for the dopamine agonist arm is questionable.

However, the principal failure of the analysis is that the most relevant comparator, the other MAO-B inhibitor, selegiline, is not considered.

## **Patient and public involvement**

Patient Interest Group Submission: Parkinson's Disease Society of the UK.

## **Budget impact**

The manufacturer estimated a budget impact for rasagiline as monotherapy in early PD on the basis of taking 10% of new eligible cases in year 1, rising to 30% by year 5; a cumulative number of patients on rasagiline of 13 in year 1 and 87 in year 5. This results in a gross cost of £10k in year 1, rising to £70k by year 5.

A net saving is anticipated due to rasagiline displacing dopamine agonists and selegiline pro-rata to their current market share. A net saving of £4,500 is anticipated in the first year, rising to £82,000 by the fifth year. However, if the appropriate comparator for and competitor with rasagiline is the other MAO-B inhibitor, selegiline, it is likely to involve an additional direct drug cost of around £800 per patient per year.

## **Guidelines and protocols**

The National Institute for Health and Clinical Excellence (NICE) is currently developing a PD clinical guideline for publication in July 2006. Draft guidance issued for consultation in August 2005 notes that it was not possible to identify a universal first choice drug therapy for people with early PD or a first choice of adjuvant drug in later PD. The choice of drugs should take account of clinical and lifestyle characteristics and the patient's preference.

## **Additional information**

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice on the 12<sup>th</sup> January 2004 that Stalevo<sup>®</sup> (levodopa, carbidopa, entacapone) tablet is accepted for use within NHS Scotland for the treatment of patients with PD and end of dose motor fluctuations not stabilised on levodopa/dopa decarboxylase inhibitor treatment. This combination preparation allows administration of a single tablet incorporating ingredients that are routinely combined for the indication described above. This may improve convenience to the patient. Depending on the doses and formulations being replaced, conversion may result in a modest increase in cost or (less commonly) a cost saving.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 16 January 2006.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The under noted references were supplied with the submission.*

*European Medicines Agency. European Public Assessment Report, Scientific Discussion (Azilect). London: EMEA, 2005.*

*Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 2002; 59: 1937–43.*

*Parkinson Study Group. A controlled, randomised, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 2004; 61: 561–6.*