Scottish Medicines Consortium

Re-Submission

rasagiline 1mg tablet (Azilect®) (No. 243/06)

Lundbeck Ltd / Teva Pharmaceuticals Ltd

10 November 2006

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 resubmission

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

Rasagiline provides modest symptomatic improvement for patients with early Parkinson's disease. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

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

Dosing information

1mg once daily

Product availability date

4th July 2005

Summary of evidence on comparative efficacy

Rasagiline is an irreversible inhibitor of the monoamine-oxidase-B (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 mechanism of action of rasagiline in Parkinson's disease (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 ≤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. 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. 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 ≥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 the delayed-treatment and rasagiline 2mg early-treatment groups 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.

There are slight differences in contra-indications listed in the Summary of Product Characteristics for rasagiline and the other MAO-B inhibitor, selegiline. These may reflect different evidence bases for drugs that have been developed many years apart.

The majority of adverse effects with rasagiline are dopaminergic reflecting its inhibition of the MAO-B enzyme. It is possible that patients who are intolerant of selegiline as a result of dopaminergic adverse effects would experience similar problems with rasagiline. It has been suggested that rasagiline may possibly have an improved adverse effect profile compared to

selegiline as it has no amphetamine-like metabolites. However, there is no evidence that this would produce clinical benefits. Similarly, it was noted in the June 2006 National Institute for Health and Clinical Excellence (NICE) guideline on PD that it is not possible from the evidence available to decide whether lack of amphetamine metabolites with rasagiline confers any clinical benefit compared to selegiline.

Summary of comparative health economic evidence

The manufacturer submitted an analysis for patients for whom selegiline is stated by the manufacturer as possibly not being the clinical treatment of choice: relatively young and/or active patients who wish to drive vehicles or operate machinery; patients with active gastric or duodenal ulcers; female patients who are taking hormone replacement therapy; patients with advanced dementia; levodopa-treated patients with severe cardiovascular disease, angina pectoris, tachycardia, arrhythmias or arterial hypertension; patients with hyperthyroidism or narrow-angle glaucoma who are receiving levodopa; patients who are experiencing, or have experienced, sleep disorders or hallucinations on dopaminergic therapy; and patients who have been prescribed selegiline but do not tolerate it. Clinical effectiveness and safety estimates for rasagiline among these patients are not available.

The manufacturer presented a Markov model implemented through a probabilistic sensitivity analysis. This modelled patients in 6-monthly cycles over 5 years within two arms:

- Starting first-line rasagiline. These patients may progress directly to levodopa, or to the second-line dopamine agonist ropinirole. Those on second-line ropinirole may then progress to levodopa.
- Starting on the first-line dopamine agonist ropinirole. These patients then progressed directly to levodopa.

The model outputs were cost and quality adjusted time to use of levodopa. The results showed that rasagiline was associated with a gain of 0.75 quality adjusted levodopa- sparing years at an additional cost of £700 compared to ropinirole. Note that the quality adjusted time to levodopa is not the same as the QALY of more conventional cost effectiveness analyses.

Treatments were 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 or levodopa were taken from the trial described previously. Other transition probabilities were interpolated from 5-year data within the literature, though the comparability of these figures is not immediately clear.

Within the analysis there was limited consideration of possible comparator regimes. Firstly, there is the exclusion of the other MAO-B inhibitor, selegiline, from the analysis through the niching of the product outlined above. In addition, there was no consideration of rasagiline second-line to the first-line dopamine agonists within the model structure. By construction the use of second-line would tend to increase the time to use of levodopa.

It also appears that the same effectiveness for the dopamine agonists has been assumed for second line treatment as for first line, and this may bias the analysis towards rasagiline. A sensitivity analysis halving this parameter reduced the net benefit of rasagiline to 0.66 quality adjusted years delay to use of levodopa.

The cost effectiveness of rasagiline monotherapy has not been demonstrated.

Summary of patient and public involvement

Additional information: guidelines and protocols

The June 2006 NICE guideline on PD recommends that levodopa, dopamine agonists and MAO-B inhibitors may be used for as symptomatic treatment for people with early PD. It was not possible to identify a universal first choice drug therapy for people with early PD and the choice of drugs should take account of clinical and lifestyle characteristics and the patient's preference.

Additional information: previous SMC advice

In February 2006, the SMC considered a full submission for rasagiline (Azilect®) and issued the following guidance, rasagiline (Azilect®) for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa) is not recommended for use within NHS Scotland. 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.

After review of an full submission, the Scottish Medicines Consortium (SMC) issued advice on 7th July 2006 that rotigotine (Neupro®) patch is not recommended for use within NHS Scotland for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa). Rotigotine was superior to placebo in two randomised controlled trials. However, in one active comparator study non-inferiority to another non-ergolinic dopamine agonist comparator was not shown. The economic case has not been demonstrated.

Additional information: comparators

One other MAO-B inhibitor, selegiline, is licensed for use as monotherapy in the UK for the treatment of 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, rotigotine and ropinirole). The NICE guideline on PD recommends that levodopa, dopamine agonists and MAO-B inhibitors may be used as symptomatic treatment for people with early PD.

Additional information: costs

Class	Drug	Daily dose range**	Annual cost (£)*
MAO-B inhibitor	**Rasagiline**	**1mg daily**	**919**
	Selegiline	10mg daily	92
Levodopa plus dopa decarboxylase inhibitor	Co-beneldopa SR	400-800mg daily+	232-465
	Co-careldopa SR	400-800mg daily+	293
	Co-careldopa	400-800mg daily+	163-221
	Co-beneldopa	400-800mg daily+	126-214
Dopamine agonist	Pramipexole	1.5-4.5 mg daily	1348-3215
	Ropinirole	9-16mg daily	1843-2327
	Rotigotine	2-8mg daily	1004-1856
	Bromocriptine	10-40mg daily	280-1122
	Pergolide	2-2.5mg daily	653-817

*costs from eVadis accessed on 16th August 2006; ** based on usual dose ranges in the 51st edition of the British National Formularly, except for pramipexole, which is the maximum possible dose range listed in the summary of product characteristics – these do not indicate therapeutic equivalence; + expressed as levodopa dose; MAO-B monoamine oxidase-B.

Additional information: budget impact

The manufacturer estimated that based upon an eligible patient population of new patients of 120 and a market penetration of 10% in year 1 rising to 30% by year 5, the gross cost of rasagiline in monotherapy would be £10K in year 1 rising to £65K in year 5. After taking account of the costs of displaced current treatments, the net cost is estimated as a saving of £5K in year 1 rising to a cumulative total saving of £97K by year 5.

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 13 October 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

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.