Scottish Medicines Consortium

rasagiline 1mg tablet (Azilect®)

Lundbeck / Teva Pharmaceuticals — No. 255/06

10 February 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 full submission

rasagiline (Azilect®) is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson's disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

Rasagiline reduces off-time in patients with Parkinson's disease and end of dose fluctuations on levodopa, similar to reductions shown with the less effective of two currently marketed catechol-O-methyl transferase inhibitors. 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 adjunct therapy (with levodopa) in patients with end of dose fluctuations.

Dosing information

1mg once daily

UK launch date

4 July 2005

Comparator medications

One other monoamine oxidase-B (MAO-B) inhibitor, selegiline, is licensed in the UK for use as an adjunct to levodopa in the treatment of Parkinson's disease (PD). Other drugs licensed for this indication include the dopamine receptor agonists (bromocriptine, cabergoline, pergolide, pramipexole and ropinirole) and the catechol-O-methyl transferase (COMT) inhibitors (entacapone and tolcapone).

Cost of relevant comparators

Class	Drug	Daily dose range**	Annual cost (£)*
MAO-B inhibitor	**Rasagiline**	**1mg daily**	**922**
	Selegiline	10mg daily	104
Dopamine agonist	Cabergoline	2-6mg daily	1515-3245
	Ropinirole	3--9mg daily	616-1848
	Pergolide	2-2.5mg daily	575-806
	Pramipexole	1.5-4.5 mg daily	1351-3500
	Bromocriptine	10-40mg daily	272-1088
COMT inhibitor	Entacapone	600-1000mg daily	657-1095
	Tolcapone	300mg daily	1042

*costs from eVadis accessed on 28th November 2005; ** based on usual dose ranges in the 50th 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; MAO-B monoamine oxidase-B; COMT catechol-O-methyl tranferase.

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.

Two double-blind trials recruited 687 and 472 adults, aged >30 years, with idiopathic PD defined by the presence of two cardinal signs (resting tremor, bradykinesia or rigidity) who experienced motor fluctuations for at least 1 hour per day (excluding morning akinesia) in the first study and for at least 2.5 hours per day in the second study, with a Hoehn and Yahr score <5 in the off-state. Before entering the study patients had been receiving optimised doses of levodopa plus dopa decarboxylase inhibitor, which were stable for at least 2 weeks and comprised at least 3 daily doses, excluding bedtime dose, with the first study excluding patients who required more than 8 daily doses. They were randomised to placebo, rasagiline 1mg once daily or a third treatment arm, which comprised entacapone 200mg with each dose of levodopa in the first study for 18 weeks and rasagiline 0.5mg once daily in the second study for 26 weeks. The primary outcome in both trials, average change in mean total daily off-time from baseline, was assessed from 24-hour patient diaries completed over 3 consecutive days before visits at weeks 6, 10, 14 and 18 in the first study and at weeks 6, 14 and 26 in the second study. These were compared between each active-treatment group and the placebo group via analysis of covariance (ANCOVA), which included baseline as covariate. In both studies, rasagiline 1mg daily significantly reduced the mean daily off-time compared to placebo, with mean (95% confidence interval (CI)) treatment effects over placebo of -0.78 hours (-1.18, -0.39) and -0.94 hours (-1.36, -0.51) in the respective trials. In the first study entacapone was also significantly superior to placebo for this outcome, with a mean (95% CI) treatment effect over placebo of -0.80 (-1.20, -0.41), similar to that in the rasagiline 1mg arm. Similar analyses were conducted for change from baseline in each active-treatment group compared to placebo for the following secondary outcomes in a hierarchical procedure (with testing only undertaken if there was a significant difference versus placebo for the previous outcome) in the order: clinical global impression of improvement (CGI) at endpoint assessed by the investigator (range -3 = markedly improved to 3 = markedly worse); change in unified PD rating scale activities of daily living subscale (UPDRS ADL) during off-time (range 0-52); and change in UPDRS motor subscale during on-time (range 0-56). In both trials significant improvement was seen in all these parameters with rasagiline 1mg daily compared to placebo. The mean (95% CI) treatment effects with rasagiline over placebo in the 26- and 18-week respective studies were: CGI -0.68 (-0.94, -0.42) and -0.49 (-0.68, -0.31); UPDRS ADL -1.34 (-2.24, -0.43) and -1.71 (-2.49, -0.93); UPDRS motor -2.87 (-4.58, -1.16) and -2.94 (-4.28, -1.60). In the active-controlled study there were significant improvements in these outcomes with entacapone compared to placebo, with treatment effects over placebo for the respective outcomes of -0.36, -1.38 and -2.73, similar to those in the rasagiline 1mg group. The second study included a fourth secondary outcome; change from baseline in PD quality of life (PDQUALIF) scale, which was not significantly different with rasagiline 1mg compared to placebo. Quality of life data collected in the other study were not provided.

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. At doses greater than this, or in combination with levodopa therapy, adverse effects were dopaminergic, with postural hypotension reported by more patients treated with levodopa plus rasagiline compared to those given levodopa plus placebo: 4.7% vs. 1.3%. Analysis of safety data from two 6-month, double-blind, placebo-controlled rasagiline trials, one described previously and one in early 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. Hallucinations were infrequent with rasagiline monotherapy but were reported more frequently among elderly patients receiving rasagiline plus levodopa (12% for patients aged ≥70 years vs. 2% for patients aged <70 years) compared to placebo plus levodopa (4% and 3% in the respective age groups). Rasagiline plus levodopa, compared to placebo plus levodopa, was associated with a greater frequency of dyskinesia: 18% vs. 10%, but, there were no age-related differences.

In the rasagiline active-controlled, double-blind trial described previously, the frequencies of dopaminergic adverse effects were similar in the rasagiline and entacapone groups, with postural hypotension reported by 2% of patients in both groups.

Summary of clinical effectiveness issues

As an adjunct to levodopa in late PD, rasagiline was compared with entacapone, a COMT-inhibitor. In indirect comparisons, entacapone appears to produce smaller improvements in on-time than the other COMT-inhibitor marketed in the UK, tolcapone, and the dopamine agonist, pramipexole. No trials directly compare rasagiline with these drugs, other drugs in these classes, or selegiline. Therefore, efficacy and safety of rasagiline relative to these drugs is uncertain.

Summary of comparative health economic evidence

The manufacturer presents the relative change in time in off-state within the active-controlled trial described previously of rasagiline against entacapone. The average value is -1 minute, with 95% CI of -22 to +25 minutes. As the minimum clinically relevant difference is deemed to be 30 minutes, this is used to justify clinical equivalence between rasagiline and entacapone. In this trial the frequencies of dopaminergic adverse events were similar in the two groups.

The dose and therefore costs of entacapone vary with daily doses of levodopa. Entacapone is less expensive than rasagiline 1mg daily when ≤4 doses of levodopa are taken daily (concomitant entacapone ≤800mg daily) and more expensive when ≥5 dose of levodopa are taken daily (concomitant entacapone ≥1000mg daily).

However, the principal weakness of the analysis is that the most relevant comparator, the other MAO-B inhibitor, selegiline, which has a considerably lower cost is not considered. The cost effectiveness of rasagiline as adjunct therapy to levodopa has not been demonstrated.

Patient and public involvement

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

Budget impact

The budget impact for rasagiline as adjunctive therapy to levodopa in late PD is estimated on the basis of rasagiline displacing 15% of the market share of new patients receiving entacapone in year 1, rising to 40% in year 5; a cumulative number of patients on rasagiline as adjunct therapy of 65 in year 1 and 454 in year 5. This results in a gross cost of £52K in the first year, rising to £505K by the fifth year.

If rasagiline displaces entacapone, as envisaged by the manufacturer, this results in a net saving of around £10K in year 1, rising to £242K in year 5. But if rasagiline displaces the other MAO-B inhibitor, selegiline, net savings will not result and an additional direct drug cost of around £800 per patient per year is likely.

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 12th January 2004 that Stalevo® (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. Those shaded grey are additional to those supplied with the submission.

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

Rascol O, Brooks DJ, Melamed E et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations. (LARGO, Lasting effect in adjunct therapy with rasagiline given once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005; 365: 947–54.

Parkinson Study Group. A randomised placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005; 62: 241–8.

Clarke CE. Rasagiline for motor complications in Parkinson's disease. Lancet 2005; 365: 914-5.