Scottish Medicines Consortium

Re-Submission

rasagiline 1mg tablet (Azilect®) (No. 255/06)

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 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. 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 adjunct therapy (with levodopa) in patients with end of dose fluctuations.

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).

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. 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 catechol-O-methyl transferase (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.

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.

Given that selegiline was not an appropriate treatment for these patients, by construction within the economic analysis, the manufacturer presented a simple cost comparison of rasagiline relative to entacapone. Both are of a similar cost.

This simple direct cost comparison relies upon rasagiline being of equivalent clinical effectiveness to entacapone. This has not been demonstrated for the above patient groups. As a consequence the cost effectiveness of rasagiline has not been demonstrated.

Summary of patient and public involvement

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

Additional information: guidelines and protocols

The June 2006 NICE guideline on PD recommends adjuvant treatment to levodopa with dopamine agonists, COMT inhibitors and MAO-B inhibitors to reduce motor fluctuations in people with later PD. It was not possible to identify a universal first choice of adjuvant drug in later PD. The choice of drug 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, rasagaline (Azilect®) for the treatment of idiopathic Parkinson's disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations is not recommended for use within NHS Scotland. 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.

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 Parkinson's disease 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.

Additional information: comparators

One other MAO-B inhibitor, selegiline, is licensed in the UK for use as an adjunct to levodopa in the treatment of PD. Other drugs licensed for this indication include dopamine receptor agonists (bromocriptine, cabergoline, pergolide, pramipexole and ropinirole) and COMT inhibitors (tolcapone and entacapone). The NICE guideline on PD recommends dopamine agonists, COMT inhibitors and MAO-B inhibitors as adjuvant treatments to levodopa to reduce motor fluctuations in people with later PD.

Additional information: costs

Class	Drug	Daily dose range**	Annual cost (£)*
MAO-B inhibitor	**Rasagiline**	**1mg daily**	**919**
	Selegiline	10mg daily	92
Dopamine agonist	Cabergoline	2-6mg daily	1511-3235
	Pramipexole	1.5-4.5 mg daily	1348-3215
	Ropinirole	9-16mg daily	1843-2327
	Bromocriptine	10-40mg daily	280-1122
	Pergolide	3mg daily	750
COMT inhibitor	Tolcapone	300mg daily	1039
	Entacapone	600-800mg daily	655-874

*costs from eVadis accessed on 16th August 2006; ** based on usual dose or 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; MAO-B monoamine oxidase-B; COMT catechol-O-methyl tranferase.

Additional information: budget impact

The manufacturer estimated that based upon an annual incidence of 358 patients who would receive entacapone, none of whom switch or die, a market share of 15% in year 1 rising to 40% of new patients in year 5 and annual per patient drug costs of £807 for rasagiline adjunct therapy, the manufacturer estimates a gross drug cost for rasagiline of £43k in year 1 rising to £417k by year 5.

With an annual per patient drug costs of £960 for entacapone, the manufacturer anticipates net savings of £8k in year 1, rising to savings of £79k 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. Those shaded grey are additional to those supplied with the submission.

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.