PUBLIC SUMMARY DOCUMENT
Product: Rasagiline, tablet, 1 mg (as mesilate), Azilect®
Sponsor: Lundbeck Australia Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The re-submission sought an Authority required (STREAMLINED) listing for Parkinson disease as adjunctive therapy in patients being treated with levodopa-decarboxylase inhibitor combinations who are experiencing fluctuations in motor function due to end-of-dose effect.

2. Background

At the July 2011 meeting, the PBAC rejected the application to list rasagiline on the PBS on the basis that the comparator was not appropriate because it did not include the pharmacological analogue, selegiline. Further, the cost-minimisation basis of the submission that flowed on from the clinical data was an insufficient basis on which to make a judgement on the cost effectiveness of rasagiline.

A copy of the Public Summary Document (PSD) from the July 2011 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-rasagiline-july11

3. Registration Status

Rasagiline was TGA registered on 6 February 2012 for the "symptomatic treatment of idiopathic Parkinson's disease (PD) as monotherapy (without concomitant levodopa/decarboxylase inhibitor) or as adjunct therapy (with concomitant levodopa/decarboxylase inhibitor therapy)."

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Parkinson disease as adjunctive therapy in patients being treated with levodopa-decarboxylase inhibitor combinations who are experiencing fluctuations in motor function due to end-of-dose effect.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Parkinson disease is a chronic, progressive, neurodegenerative disease which causes the neurons in the substantia nigra cells to die, leading to a lack of dopamine in the brain, especially in the basal ganglia. This results in loss of ability to control normal body movements, with varying degrees of muscular control. Patients with advanced Parkinson disease experience daily changes in symptoms, medication side effects that limit treatment and the loss of independence in activities of daily living.

The re-submission proposed that the place in therapy of rasagiline was as an alternative to entacapone as adjunctive therapy in patients receiving levodopa-decarboxylase inhibitor combination therapy but experiencing motor fluctuations due to end-of-dose effect.

6. Comparator

The resubmission presented a mixed comparator of entacapone and selegiline.

For PBAC's view see Recommendation and Reasons.

7. Clinical Trials

The basis of the re-submission was one three-arm randomised trial (LARGO) pre-specified to compare rasagiline with placebo, with additional post-hoc analyses comparing rasagiline directly with the active entacapone control arm. This was unchanged from the previous submission. The submission also presented an indirect comparison of rasagiline and entacapone using three (LARGO, PRESTO and Rabey 2000) randomised comparative trials comparing rasagiline with placebo and seven randomised comparative trials comparing entacapone with placebo. Publication details have been previously reported in the July 2011 PSD.

The scientific basis of the comparison for rasagiline with selegiline was based on an indirect comparison of the LARGO, PRESTO and Rabey 2000 trials and four trials comparing selegiline with placebo (Presthus 1983, Golbe 1988, Takahashi 1994, Weng 2002) in patients with Parkinson disease experiencing motor fluctuations who were receiving levodopa therapy. Most of the trials for selegiline were of short duration (six to eight weeks study treatment duration) and had been conducted between 1983 and 2002. The primary outcome for the LARGO and PRESTO trials was change in mean total daily 'OFF' time, the primary outcome in Rabey 2000 was safety and tolerability, while none of the selegiline trial publications specified the primary outcome measure.

Publication details of the trials comparing selegiline with placebo are presented in the following table.

Trial ID/ First author	Protocol title/Publication title	Publication citation
Selegiline vs placebo		
Presthus J et al, 1983	Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease.	Acta Neurol Scand Suppl 1983; 95: 127-33.
Golbe LI et al, 1988	Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease.	Clin Neuropharmacol 1988; 11(1): 45-55.
Takahashi M et al, 1994	Selegiline (L-deprenyl) and L-dopa treatment of Parkinson's disease: A double-blind trial.	Intern Med 1994; 33(9): 517-24.
Weng ZF et al, 2002	Clinical efficacy of selegiline added to levodopa/decarboxylase inhibitor in Parkinson's disease.	Journal of Modern Nervous Diseases 2002; 2: 281-4.

8. Results of Trials

The pooled analysis of data from the LARGO and PRESTO studies showed a statistically significant decrease of just under one hour in total daily OFF time favouring rasagiline (weighted mean difference:-0.89; 95% CI: -1.21 to -0.58, $p<0.0001$) compared to placebo.

Improvement in symptoms based on the Unified Parkinson's Disease Rating Scale (UPDRS) in the "ON" state was reported in LARGO, PRESTO, and Rabey 2000 trials, with a pooled analysis (excluding the Rabey results) showing a reduction in the Total UPDRS score in ON

state significantly favouring rasagiline (weighted mean difference -2.90; 95% CI: -4.21 to -1.60, p<0.0001). Pooled clinical global assessments of improvement during "ON" state were estimated from the LARGO and PRESTO trials, with a weighted mean difference score of -0.54 (95% CI: -0.69 to -0.39) in favour of rasagiline.

Both the Presthus 1983 and Weng 2002 trials found a similar significant reduction in Webster Rating Scale total score (of approximately 30%) favouring selegiline plus levodopa over placebo plus levodopa.

Pooled analysis of investigator clinical global improvement scores showed that 73% of patients on selegiline versus 33% of patients on placebo showed at least minimum improvements (OR:5.85; 95% CI 3.06 to 11.19, p<0.003).

In the indirect comparison of rasagiline with levodopa versus selegiline with levodopa, the only common measure that allowed a quantitative indirect comparison was the change in levodopa dosage over the trial period.

The quantitative indirect comparison showed a significant difference between rasagiline and selegiline in this measure, with greater reduction in levodopa dosage with selegiline (weighted mean difference = 230 mg/d [95% CI 31.8, 427.3], p=0.02). However, as there were differences in protocol for levodopa changes between the two trials, the relevance of this indirect comparison was questionable.

Both rasagiline and selegiline as adjunctive therapy to levodopa appeared to have some benefit on the individual outcomes. The clinical trials for rasagiline reported different efficacy outcomes compared to the selegiline trials, which reduced the confidence of assessing the relative efficacy of rasagiline and selegiline as adjunctive therapy to levodopa using placebo as a common comparator.

The incidence of adverse events between rasagiline and entacapone treated patients in the LARGO trial have been previously reported in the July 2011 PSD.

In a quantitative indirect comparison of rasagiline versus selegiline of the adverse events and treatment withdrawals due to adverse events, both rasagiline and selegiline as adjunctive therapy were associated with pooled higher (non-statistically significant) rates of adverse events compared to placebo as adjunctive therapy. There was large variability in the event rates across the different trials, and as such the indirect comparison should be interpreted with caution. Both rasagiline and selegiline with levodopa did not increase the withdrawal rate due to adverse events.

Rasagiline treatment adverse events that occurred at a rate ≥ 5% (versus placebo) were accidental injury, postural hypotension, dyskinesia, and arthralgia. Selegiline treatment adverse events that occurred at a rate ≥ 5% (versus placebo) were nausea, depression, dizziness/light-headedness, confusion, insomnia, and auditory hallucination. Common treatment-emergent adverse events that occurred at a rate ≥ 5% (versus placebo) across both rasagiline and selegiline were vomiting, weight loss and anorexia. Due to variability in data collection and reporting methods, and the small size of some of the trials, it was appropriate that no quantitative comparison of treatment-emergent adverse events was performed in the resubmission.

The UK Parkinson's disease Research Group (1998) concluded that falls and dementia were more common in the selegiline and levodopa treatment arm, and that use of selegiline should be avoided in patients with postural hypotension, frequent falls, confusion and dementia.

9. Clinical Claim

The re-submission claimed that the efficacy and safety of rasagiline was non-inferior to selegiline as well as entacapone.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as rasagiline 1 mg daily and entacapone 953 mg daily. The equi-effective dose for rasagiline and selegiline is rasagiline 1 mg daily and selegiline 10 mg daily, based on two of the four selegiline trials, Golbe 1988 and Presthus 1983.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated in the re-submission to be between 10,000 and 50,000 in Year 5, at a net cost per year to the PBS of less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended listing of rasagiline 1 mg tablet on the PBS as an Authority Required (STREAMLINED) listing for Parkinson disease.

The basis for the recommendation was cost-minimisation primarily against selegiline. The equi-effective doses were considered to be rasagiline 1 mg daily and selegiline 10 mg daily. Entacapone was accepted only as a secondary comparator, and the PBAC rejected any approach to cost-minimisation in which entacapone contributed a greater weight than selegiline. If entacapone did contribute to the cost-minimisation, the equi-effective doses were rasagiline 1 mg daily and entacapone 953 mg daily. The PBAC also noted that the ESC had questioned the lower substitution rates for pramipexole as a third relevant comparator for rasagiline. Pramipexole had a larger existing market share than entacapone. An alternative approach that would be appropriate for calculation of the cost-minimisation would include the full range of drugs that could possibly be substituted, weighted primarily by existing market share.

The PBAC considered that for the listing as originally proposed, the most appropriate comparator was selegiline. This was in accordance with the Guidelines, which stated that "if the proposed drug is in a therapeutic class for which pharmacological analogues are already listed, the main comparator would usually be the analogue that is prescribed on the PBS for the largest number of patients". However, the PBAC considered that a listing simply for Parkinson disease was more appropriate, noting the comment in the Pre-PBAC Response from the sponsor that, if the restriction were simplified to Parkinson disease, this would allow use as monotherapy. The PBAC noted that rasagiline was TGA-approved for both monotherapy and adjunctive therapy, and that use as monotherapy outside the requested

restriction of "adjunctive therapy" would have been anticipated. Therefore, the PBAC considered that a pragmatic way forward, based on clinical need, would be to list rasagiline for "Parkinson disease", which would allow monotherapy use of rasagiline. On this basis, a mixed comparison with entacapone and potentially pramipexole would be reasonable. These products would likely to be replaced by rasagiline as well as selegiline.

The PBAC accepted that rasagiline was non-inferior to entacapone based on the post-hoc analyses of LARGO and the indirect comparison using three (LARGO, PRESTO and Rabey 2000) randomised comparative trials comparing rasagiline with placebo and seven randomised comparative trials comparing entacapone with placebo. The PBAC noted that there was also an indirect comparison of rasagiline with selegiline using three trials comparing rasagiline with placebo (LARGO, PRESTO, Rabey 2000) and four trials comparing selegiline with placebo (Presthus 1983, Golbe 1988, Takahashi 1994, Weng 2002) in patients with Parkinson disease experiencing motor fluctuations who are currently receiving levodopa therapy. The PBAC noted that the trials had many differences including the use of different primary outcome measures, there was limited information on patient characteristics, the selegiline trials were older (1983-2002) and that levodopa dosage adjustment schedules were different between the trials. The PBAC noted that the only common measure that allowed a quantitative indirect comparison was the change in levodopa dosage over the trial period and that this showed a significant difference between rasagiline and selegiline in this measure, with greater reduction in LD dosage with selegiline (WMD (Weighted Mean Dose) = 230 mg/d [95% CI 31.8, 427.3], p=0.02). As both drugs demonstrated reductions in levodopa dosage, given the differences in the trial populations and the fact that the comparison was indirect, the PBAC considered that it would be highly likely that rasagiline was non-inferior to selegiline and that non-inferiority be accepted between these two MAO-B inhibitors.

In making this recommendation the PBAC noted the consumer comments on this item.

The PBAC recommended that rasagiline was suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

Recommendation:
RASAGILINE, tablet, 1 mg (as mesilate)

Restriction: Authority Required (STREAMLINED)
Parkinson Disease

Note
Continuing Therapy Only:
For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Note
No applications for increased maximum quantities and/or repeats will be authorised.

Max quantity: 30
Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor chose to make no further comment.