PUBLIC SUMMARY DOCUMENT
Product: RASAGILINE, tablet, 1 mg, Azilect®
Sponsor: Lundbeck Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority required (Streamlined) listing for the treatment of 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

This drug had not previously been considered by the PBAC.

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 therapy) 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. The PBAC considered the requested restriction appropriate.

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.

The submission proposed that the place in therapy of rasagiline is 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 submission nominated entacapone as the main comparator. The main arguments for the nomination are summarised below:

- rasagiline has the same proposed PBS indication as entacapone.
- rasagiline was tested in patients with similar characteristics to entacapone.
- the Australian treatment survey conducted by the submission suggested that entacapone is used frequently for motor fluctuations due to end dose effect of levodopa. PBS utilisation data also supports the contention that entacapone is the most widely used adjunctive therapy.

The PBAC did not agree that this was the appropriate comparator. *See Recommendation and Reasons.*

7. Clinical Trials

The basis of the submission was one three-arm randomised trial pre-specified to compare rasagiline with placebo, with additional post-hoc analyses comparing rasagiline directly with the active entacapone control arm (LARGO).

The submission also presented an indirect comparison of rasagiline and entacapone using three randomised comparative trials (LARGO, PRESTO and Rabey 2000) comparing rasagiline with placebo, and seven randomised comparative trials comparing entacapone with placebo. Each rasagiline trial included patients with PD and motor fluctuations and assessed the use of 1 mg per day rasagiline in addition to levodopa. The entacapone trials also included patients with PD and motor fluctuations and assessed the use of, on average, 935 mg per day entacapone in addition to levodopa (entacapone 200mg was taken with each levodopa dose).

Details of the trials published at the time of the submission are in the table below.

Trial	Protocol title/ Publication title	Publication citation
Direct comparison		
Rasagiline vs entacapone		
LARGO (post-hoc analysis) Rascol O, 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.	*The Lancet 2005;* 365(9463): 947-54,
Indirect comparison (Placebo as common reference)		
Rasagiline		
LARGO (pre-specified analysis)	As above	As above
PRESTO Parkinson Study Group	A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study.	*Arch Neurol 2005;* 62(2):241-8.
Rabey 2000	Rasagiline Mesylate, a New Mao-B Inhibitor for the Treatment of Parkinson's Disease: A Double-Blind Study as Adjunctive Therapy to Levodopa.	*Clinical* N*europharmacology 2000;* 23 (6):324–330.
Entacapone		
Poewe 2002	Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal Levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study).	*Acta Neurol Scand 2002;* 105: 245-255.
Reichmann 2005	Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-OFF type fluctuations.	*Acta Neurol Scand 2005:* 111: 21–28.
Myllyla 2001	Twelve-month safety of entacapone in patients with Parkinson's Disease.	*European Journal of Neurology 2001;* 8:53-60.
Fenelon 2003	Efficacy and tolerability of entacapone in patients with	*J Neural Transm 2003;* 110:

	Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-OFF motor fluctuations. A randomized, double-blind, multicentre study.	239–251.
Rinne 1998	Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations.	*Neurology 1998;* 5 1: 1309-1314.
PSG 1997	Parkinson Study Group. Entacapone Improves Motor Fluctuations in Levodopa-Treated Parkinson's Disease Patients.	*Ann Neurol 1997;* 42:747-755.
Brooks 2003	Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's Disease: a randomised, placebo controlled, double blind, six month study.	*J Neurol Neurosurg Psychiatry 2003;* 74: 1071-1079.

8. Results of Trials

The table below summarises the results of the primary outcome of the LARGO trial. As stated above, the comparison of rasagiline and entacapone was conducted post-hoc, thus the trial may not have been powered to detect a difference between treatments. The power calculations for the LARGO trial were based on the primary endpoint, the change from baseline in the mean total daily "OFF" time, as measured through subject daily '24-hour' diaries at baseline and during treatment. A difference between changes of the placebo-treated arm and the active treatment arm of 45 minutes or more was considered as a change of clinical importance.

Main results from the LARGO trial for the mITT populations

Outcomes	**PBO N=218**	**ENT N=218**	**RAS N=222**
Primary Outcome: Change from baseline in mean daily 'OFF' time (hours)			
Baseline	5.50	5.60	5.60
Endpoint	5.10	4.40	4.42
Change (95%CI)	-0.40 (-0.69, -0.10)	-1.20 (-1.49, -0.90)	-1.18 (-1.47, -0.88)
Difference v PBO (95% CI, p value)		**-0.80 (-1.20, -0.41) p<0.0001**	**-0.78 (-1.18, -0.39) p=0.0001**
Difference RAS v ENT (95% CI, p value) Post-hoc			0.02 (-0.37, 0.42) P=0.92

Abbreviations: RAS = rasagiline, ENT = entacapone, PBO= placebo; mITT = modified intention-to-treat (primary endpoint analysis undertaken on all patients with at least one post-randomisation measurement (or diary) for that endpoint)
Bolded typography indicates statistically significant differences between groups

For the primary outcome of the LARGO trial, rasagiline treatment was associated with statistically significant reductions in mean daily "OFF" time versus placebo, a difference of -0.78 hours (95% CI: -1.18, -0.39; p=0.0001). Forty-five minutes is considered a clinically important difference between rasagiline and placebo. The reduction in OFF time as expressed in minutes is (-46.8; 95% CI: -70.8, -23.4), thus although statistically significantly different, the results may not indicate a clinically significant difference between rasagiline and placebo as the reduction in OFF time could be as little as 23 minutes. The reduction in OFF time was of similar magnitude to that observed for entacapone versus placebo (difference (95% CI): -0.80 hours (-1.20, -0.41); p<0.0001). This expressed in minutes is

(-48.0; 95% CI: -72.0, -24.6). When comparing rasagiline to entacapone, in post-hoc analyses, there was no statistically significant difference between the two treatment groups (difference (95% CI): 0.02 (-0.37, 0.42), however the trial may not have been powered to detect any differences. This difference expressed in minutes is (1.2; 95% CI: -22.2, 25.2). The upper limit of 0.42 translates into a reduction in OFF time of approximately 25 min per day less for rasagiline versus entacapone. The results for the reported secondary outcomes similarly did not demonstrate any differences between treatments.

The results of the indirect comparison of rasagiline and entacapone, using placebo as the common reference were generally consistent with those of the post-hoc analysis of the LARGO trial. The placebo response rates across the trials varied substantially. As for the LARGO trial, these analyses were all conducted post-hoc.

The submission provided no data assessing the comparative effectiveness and safety of rasagiline versus selegiline.

The incidence of adverse events between rasagiline and entacapone treated patients in the LARGO trial were similar and did not significantly differ between the two groups, with the exception of cardiovascular system adverse events that were slightly higher for rasagiline versus entacapone treatment (RD (95%CI): 0.06 (0.01, 0.12)). There were no statistically significant differences between rasagiline and entacapone treatment from the indirect comparison of the included trials. A summary of the periodic safety update report (PSUR) covering 3 Jan 2009 to 2 Jan 2010 was provided with the submission. No new signals of concern or changes to the company core data sheets (and thus the draft Product Information) were deemed necessary.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described rasagiline as non-inferior in terms of comparative effectiveness and comparative safety over 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 and entacapone 953 mg, based on the doses in the LARGO trial.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost to the PBS of less than $10 million in year 5 of listing.

12. Recommendation and Reasons

The PBAC agreed that the requested restriction is appropriate and is consistent with the trial evidence.

The PBAC considered that the submission's nomination of entacapone as the sole main comparator was inappropriate as selegiline is a pharmacological analogue of rasagiline.

The PBAC noted the sponsor's argument that selegiline is used in a different population than rasagiline. However, the PBAC considered that it remains unclear whether 'motor fluctuations' were a symptom associated with late stage Parkinson disease, and therefore there may be some overlap in patients with motor fluctuations and those classified as having late stage disease. Therefore this argument was not considered to provide sufficient justification for the exclusion of selegiline from consideration as a comparator. Therefore the PBAC considered that a comparison with selegiline would be necessary.

The PBAC acknowledged that entacapone appears to be more widely used than selegiline, and that rasagiline is likely to substitute to some extent for entacapone, and therefore considered that a mixed comparator, comprising both entacapone and selegiline might be appropriate.

The PBAC noted that there had previously been concerns around increased risk of melanoma with rasagiline, but considered that these concerns had been appropriately resolved, and that at this time this issue is not relevant.

The submission presented 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. The results of LARGO showed no difference in off time for patients treated with rasagiline compared to entacapone. The PBAC considered that based on the LARGO study the claim of non-inferiority to entacapone was reasonable, however, as noted above, this comparison was not considered the only evidence that was relevant in the absence of any comparison with selegiline.

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 flows on from the clinical data is an insufficient basis on which to make a judgement on the cost effectiveness of rasagiline.

The PBAC noted the consumer comments received in its consideration of rasagiline.

Recommendation:
Reject

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 has no comment.