

5.13 SAFINAMIDE, Tablet, 50 mg, 100 mg, Xadago™, Seqirus

1 Purpose of Application

- 1.1 The submission requested a Restricted Benefit listing for safinamide for treatment of Parkinson’s disease (PD), as add-on therapy to levodopa in patients experiencing motor fluctuations. This is the first consideration of safinamide by the PBAC.
- 1.2 The requested listing was based on a cost-minimisation analysis of safinamide to rasagiline based on the rasagiline price prior to the application of the 5% statutory price reduction on 1 April 2018. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with PD being treated with levodopa alone or in combination with other PD medications who are experiencing motor fluctuations.
Intervention	Safinamide 50 mg or 100 mg once per day
Comparator	Rasagiline 1 mg tablet once per day.
Outcomes	Increase in ON time without troublesome dyskinesia; change in OFF time; change in UPDRS Section II and Section III scores during ON time; AEs; discontinuations due to AEs; serious AEs; and deaths.
Clinical claim	In fluctuating PD patients treated with levodopa, safinamide is non-inferior to rasagiline in terms of both efficacy and safety. This was not demonstrated for the safinamide 50 mg dose for some of the outcomes* noting the inherent limitations of an indirect comparison.

*Non-inferiority was not demonstrated for safinamide 50 mg/day compared to rasagiline 1 mg/day in terms of increase in ON time without troublesome dyskinesia and improvement in UPDRS section III motor examination during ON time.

AEs = adverse events; PD = Parkinson’s disease; UPDRS = Unified Parkinson’s Disease Rating Scale.

Source: Table 1.1.1, p30 of the submission

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity ^a	Proprietary name and manufacturer
SAFINAMIDE					Xadago (Seqirus)
Tablet 50 mg	1	30	5	\$ [REDACTED]	
Tablet 100 mg	1	30	5	\$ [REDACTED]	

Category /Program	<i>GENERAL – General Schedule (Code GE)</i>
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

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Episodicity:	Chronic
Severity:	N/A
Condition:	Parkinson's disease
PBS Indication:	Parkinson's disease
Restriction:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be as add-on therapy to a levodopa-decarboxylase inhibitor combination, AND Patient must be experiencing motor fluctuations.
Administrative Advice:	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
Notes:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

- 2.2 The requested restriction appears broadly consistent with the proposed TGA indication. However, it is unclear whether the requested restriction is adequate in terms of consistency with issues raised during the TGA evaluation of safinamide, relating to specification of mid-to-late stage PD and a requirement for a “stable dose” of levodopa in the proposed indication. The Pre-Sub-Committee Response (PSCR, p 4-5) stated that mid to late disease stage is not standard terminology in this area and would be open to variable interpretation. The ESC considered that it would not be clinically appropriate to specify the disease stage in the restriction as patients often experience sub-clinical disease for a number of years prior to diagnosis, therefore at the time of diagnosis, all patients could well be considered as having mid to late stage disease.
- 2.3 Similarly, the ESC considered that virtually all patients with diagnosed Parkinson’s Disease seeking treatment would have some degree of motor fluctuations, so specifying this in the clinical criteria would unlikely be clinically meaningful.
- 2.4 The PSCR (p 4-5) disagreed with the Secretariat suggested restriction as the concept of a stable levodopa dose is difficult to define and does not reflect clinical practice. The ESC agreed with the PSCR and considered that including the requirement for patients to be on a stable levodopa dose in the restriction would be open to interpretation and would unlikely be clinically meaningful.
- 2.5 The pre-PBAC response noted that the TGA delegate has agreed to remove the reference to mid to late stage disease and stable dose of levodopa from the indication. The pre-PBAC response also noted that the sponsor agreed with the wording proposed by the ESC, which is consistent with the anticipated indication. The PBAC foreshadowed that the requested restriction would be consistent with the expected TGA indication and considered that it would be appropriate to exclude the criteria for disease stage, stable levodopa dose and motor fluctuations as advised by the ESC.

- 2.6 The recommended dosing regimen in the draft Product Information (PI) is to start safinamide at a dose of 50 mg/day which may be increased to 100 mg/day, after two weeks, on the basis of individual clinical need. During the second round of the TGA evaluation, the sponsor proposed an amendment to the recommended dosing regimen in the draft PI that the initial 50 mg/day safinamide dose should be increased by default to 100 mg/day unless tolerability issues prevent this (the default dose would change from 50 mg/day to 100 mg/day). The ACM resolution that became available during the evaluation (ACM Ratified Resolution of meeting 10, August 2018, Item 2), noted that there was unclear evidence of a predictable dose-response relationship (between the 50 mg and 100 mg daily doses) and suggested a subsequent down-titration from 100 mg/day if further improvement has not been demonstrated. Neither Study 016 nor SETTLE fully reflect these doses and/or titration recommendations:
- Study 016 had two safinamide treatment arms: a fixed 50 mg/day arm and a fixed 100 mg/day arm.
 - Patients in SETTLE initiated safinamide treatment at 50 mg/day and up-titrated in two weeks to 100 mg/day (where tolerability allowed), which is consistent with the proposed amendment to the draft PI by the sponsor. However, no down-titration was allowed in this study. The applicability of the results of this study will depend on the doses approved by the TGA.
- 2.7 The PSCR (p1) noted that the final PI is expected to specify safinamide treatment should be started at 50 mg/day and may be increased to 100 mg/day after two weeks on the basis of individual clinical need. The ESC noted that the proportion of patients who would remain on the 50 mg dose in clinical practice is uncertain.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of the PBAC consideration, a draft Product Information (PI), the second round TGA evaluation report (with a sponsor-proposed amendment to dosing instructions in the draft PI), the TGA Delegate's Overview, and the ACM Ratified Resolution, were available.
- 3.2 The amended indication based on advice in the ACM ratified resolution was: "for the treatment of adult patients with mid to late stage idiopathic Parkinson's disease with motor fluctuations, as add-on therapy to a regimen that includes a stable levodopa (L-dopa) dose."
- 3.3 The pre-PBAC response noted that the TGA Delegate agreed to remove the terms "mid-to-late" and "stable dose" from the indication and indication now reads: Xadago™ is indicated for the treatment of adult patients with fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes levodopa (L-Dopa).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 PD is a major neurodegenerative disorder in which a progressive loss of nigrostriatal dopaminergic neurons leads to a set of motor symptoms, including resting tremor, rigidity, bradykinesia and postural instability.
- 4.2 As PD progresses, most people will develop motor symptoms and will be treated with levodopa. Other treatments may be needed for people whose PD is not adequately controlled on levodopa alone, with the aim of reducing motor complications and improving quality of life (QoL). These therapies include dopamine agonists, monoamine oxidase-B (MAO-B) and catechol-O-methyl transferase (COMT) inhibitors.
- 4.3 Safinamide is a third generation MAO-B inhibitor with high selectivity for MAO-B over MAO-A and its non-covalent, reversible inhibition.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated rasagiline as the main comparator, since rasagiline (a second generation MAO-B) is a pharmacological analogue of safinamide and is the most likely therapy to be replaced in clinical practice should safinamide be listed on the PBS. The submission considered that rasagiline was a more appropriate main comparator for safinamide than selegiline as PBS usage data showed selegiline is now very rarely used with declining prescription numbers due to a number of limitations related to its safety profile. The evaluation noted that this may be reasonable given the lower selectivity of selegiline (compared to rasagiline) for MAO-B over MAO-A (particularly at high doses), its amphetamine and methamphetamine metabolites and other potential cardiac and psychiatric side effects. However, some substitution for selegiline may be possible in some late stage PD patients.
- 5.2 The ESC considered that rasagiline was an appropriate comparator. The ESC noted that rasagiline can be used as monotherapy and has a broader indication than safinamide. The PBAC noted that rasagiline was recommended for listing on a cost minimisation basis compared to selegiline as the primary comparator and to entacapone as a secondary comparator and that selegiline is currently substantially less expensive than rasagiline.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison between safinamide and rasagiline via placebo as the common reference using:

- Two 24-week randomised trials (Studies 016 and SETTLE) comparing safinamide with placebo in levodopa-treated PD patients experiencing motor fluctuations. Study 016 had two fixed safinamide-dose arms (50 and 100 mg/day) and SETTLE had a safinamide-dose arm that could be adjusted within the range 50-100 mg/day. The majority of patients in SETTLE were subsequently administered the 100 mg/day dose.
- Seven randomised trials (PRESTO, LARGO, Zhang, Hauser, Hattori, CHORAL and 13484A) with different follow-up periods (ranging from 12 weeks to 26 weeks) comparing rasagiline with placebo (some studies included additional active comparator arms) in levodopa-treated PD patients.

6.4 Although several indirect comparisons were presented in the submission, indirect analyses of an outcome measured by a similar method were limited to a few of the rasagiline trials. For example, the comparison between safinamide and rasagiline, using the E method of measuring change in ON time, could include only two of the seven rasagiline studies (Hauser and Zhang).

6.5 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Safinamide versus placebo		
Study-016	A phase 3, double-blind, randomised placebo-controlled study to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of safinamide, as add-on therapy, in patients with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, and/or an anticholinergic. Borgohain R, Szasz, J., Stanzione, P, Meshram, C, Bhatt, M, Chirilineau, D., Stocchi, F., Lucini, V., Giuliani, R., Forrest, E., Rice, P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. 2014; 29: 229–237.	<i>Movement Disorders</i> . 2014; 29:229-237. <i>58th Annual Meeting of the American Society of Hematology (ASH) Blood</i> . 2016; 128:234

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Trial ID	Protocol title/ Publication title	Publication citation
SETTLE	<p>A phase III, double-blind, randomised placebo-controlled, randomized trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of safinamide, as add-on therapy, in subjects with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine.</p> <p>Schapira AHV, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations. A randomized clinical trial. 2017;74(2):216-224.</p> <p>Cattaneo C, Sardina M, Bonizzoni E. Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: Post hoc analyses of studies 016 and SETTLE (Cattaneo et al., 2016)</p> <p>Cattaneo C, Barone P, Bonizzoni E, Sardina M. Effects of safinamide on pain in fluctuating Parkinson's disease patients: A post-hoc analysis. (Cattaneo et al., 2017a)</p>	<p><i>JAMA Neurol.</i> 2017; 74(2): 216-224.</p> <p><i>Journal of Parkinson's Disease.</i> 2016;6(1):165-173</p> <p><i>Journal of Parkinson's Disease.</i> 2017; 7(1):95-101.</p>
Supplementary evidence on long term efficacy of safinamide versus placebo		
Study 018	<p>A phase 3, double-blind, Placebo-controlled, 18-month extension study to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of safinamide, as add-on therapy, in patients with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, and/or an anticholinergic.</p> <p>Borghain, R., Szasz, J., Stanzione, P., Meshram, C., Bhatt, M. H., Chirilineau, D., Stocchi, F., Lucini, V., Giuliani, R., Forrest, E., Rice, P., Anand, R. and the Study 018 Investigators. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease</p> <p>Cattaneo C, Ferla RL, Bonizzoni E, Sardina M. Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's disease: A post-hoc analysis.</p> <p>Cattaneo C, Kulisevsky J, Tubazio V, Castellani P. Long-term efficacy of safinamide on Parkinson's disease chronic pain.</p>	<p><i>Movement Disorders.</i> 2014; 29: 1273-1280.</p> <p><i>Journal of Parkinson's Disease.</i> 2015;5(3):475-481.</p> <p><i>Adv. Ther.</i> 2018; 35:515-522.</p>
Rasagiline versus placebo		
PRESTO	<p>Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study.</p> <p>deMarcaida J. A., Schwid, S. R., White, W. B., Blindauer, K., Fahn, S., Kieburz, K., Stern, M. and Shoulson, I. Effects of tyramine administration in Parkinson's disease patients treated with selective MAO-B inhibitor rasagiline'</p> <p>Elmer L, Schwid S, Eberly S, Goetz C, Fahn S, Kieburz K, et al. Rasagiline-associated motor improvement in PD occurs without worsening of cognitive and behavioural symptoms.</p>	<p><i>Arch Neurol.</i> 2005; 62(2):241-248.</p> <p><i>Movement Disorders.</i> 2006; 21(10) 1716-1721.</p> <p><i>Journal of the Neurological Sciences.</i> 2006; 248(1-2):78-83.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Goetz CG, Schwid SR, Eberly SW, Oakes D, Shoulson I. Safety of rasagiline in elderly patients with Parkinson disease</p> <p>White WB, Salzman P, Schwid SR. Transtelephonic home blood pressure to assess the monoamine oxidase-B inhibitor rasagiline in Parkinson disease.</p>	<p><i>Neurology</i>. 2006;66(9):1427-1429.</p> <p><i>Hypertension</i>. 2008; 52(3):587-593.</p>
LARGO	<p>Randomised placebo controlled 18-week, study of rasagiline or entacapone as adjuncts to levodopa for patients with Parkinson disease. Lasting effect in adjunct therapy with rasagiline given once daily (LARGO):</p> <p>Rascol O, Brooks DJ, Melamed E, et al; LARGO study group. 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</p> <p>Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, et al. Validation of the freezing of gait questionnaire in patients with Parkinson's disease.</p> <p>Stocchi F, Rabey JM. Effect of rasagiline as adjunct therapy to levodopa on severity of OFF in Parkinson's disease.</p> <p>Elmer LW. Rasagiline adjunct therapy in patients with Parkinson's disease: post hoc analyses of the PRESTO and LARGO trials.</p> <p>Tolosa E, Stern MB. Efficacy, safety and tolerability of rasagiline as adjunctive therapy in elderly patients with Parkinson's disease. ¹</p> <p>Lew MF. Rasagiline treatment effects on parkinsonian tremor.</p> <p>Perez-Lloret, S., and O. Rascol. Safety of rasagiline for the treatment of Parkinson's disease, <i>Expert Opinion on Drug Safety</i>, 2011; 10: 633-43.</p>	<p><i>Lancet</i>. 2005; 365 (9463):947-954.</p> <p><i>Movement Disorders</i>. 2009; 24(5):655-661.</p> <p><i>European Journal of Neurology</i>. 2011; 18(12):1373-1378.</p> <p><i>Parkinsonism & Related Disorders</i>. 2013; 19(11):930-6.</p> <p><i>European Journal of Neurology</i>, 2012; 19(2):258-64.</p> <p><i>International Journal of Neuroscience</i>. 2013; 123(12):859-65.</p>
Zhang	<p>Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial.</p>	<p><i>Int J Neuropsychopharmacol</i>. 2013;16(7):1529-37.</p>
Hauser	<p>Hauser RA, Stocchi F, Rascol O, Huyck SB, Capece R, Ho TW, et al. Preladenant as an adjunctive therapy with levodopa in Parkinson disease: two randomized clinical trials and lessons learned</p> <p>A placebo- and active controlled study of preladenant in subjects with moderate to Severe Parkinson's Disease (P04938) (ClinicalTrials.gov Identifier: NCT01155466)</p>	<p><i>JAMA Neurology</i>. 2015; 72(12):1491-1500.</p>
Hattori	<p>Hattori N, Takeda A, Takeda S, Nishimura A, Kato M, Mochizuki H, et al. Efficacy and safety of adjunctive rasagiline in Japanese Parkinson's disease patients with wearing-off phenomena: A phase 2/3, randomized, double-blind, placebo-controlled, multicenter study.</p>	<p><i>Parkinsonism & Related Disorders</i>. 2018 <i>in press</i>. ²</p>
CHORAL	<p>Azilect (rasagiline) in levodopa-treated Parkinson's disease patients with motor fluctuations in China (CHORAL)</p>	<p>ClinicalTrials.gov Identifier: NCT01479530</p>
13484A	<p>Study of Azilect (rasagiline) in levodopa-treated Parkinson's disease patients with motor fluctuations in Korea.</p>	<p>ClinicalTrials.gov Identifier: NCT01268891</p>

Source: Table 2.2.1-2.2.2, pp53-59 of the main submission.

6.6 Study 018 was an extension of Study 016 and not used in the indirect comparison analysis due to its substantially longer follow-up (18 months or ~78 weeks) and a different primary outcome measure (mean change in the Dyskinesia Rating Scale (DRS)) compared to the other included safinamide and rasagiline trials. The rasagiline Zhang study was only included in sensitivity analyses for efficacy outcomes as the submission considered the study to have “poorly defined and incoherently and inconsistently reported efficacy outcomes”.

6.7 The key features of the included evidence for the indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Trial	N*	Design/ duration	Risk of bias**	Patient population	Outcomes [Method of measurement]
Safinamide vs. placebo					
STUDY 016	669	R, DB 24 weeks	Low	PD patients with motor fluctuation on stable/optimised dose of levodopa prior to enrolment	Increase in daily ON time without troublesome dyskinesia [E]; Decrease in daily OFF time [E]*
SETTLE	549	R, DB 24 weeks	Low	As above	As above
Rasagiline vs. placebo					
LARGO	460	R, DB 18 weeks	Low	As above	Increase in daily ON time without troublesome dyskinesia [A]; Decrease in daily OFF time [A, E]
Hattori	270	R, DB 23 weeks	Unclear	As above	Increase in daily ON time without troublesome dyskinesia [A]; Decrease in daily OFF time [A, E]
CHORAL	321	R, DB 16 weeks	Unclear	As above	Decrease in daily OFF time [A]
13484A	132	R, DB 18 weeks	Unclear	As above	Decrease in daily OFF time [A]
PRESTO	308	R, DB 26 weeks	Low	As above	Increase in daily ON time without troublesome dyskinesia [A]; Decrease in daily OFF time [A, E]
Hauser	311	R, DB 12 weeks	Unclear	As above	Increase in daily ON time without troublesome dyskinesia [E]; Decrease in daily OFF time [E]
Zhang	244	R, DB 12 weeks	Unclear	PD patients with motor fluctuations (unclear whether stable/optimised levodopa dose)	Increase in daily ON time without troublesome dyskinesia [E]; Decrease in daily OFF time [E]

DB=double blind; R=randomised.

* In rasagiline studies, only the number of patients in the relevant comparison arms (rasagiline 1mg and placebo) is presented.

** Overall, the risk of bias in the indirect comparisons is high due to clinical heterogeneity across the studies

End-of-treatment analysis [E]: Increase in mean daily ON time without troublesome dyskinesia and decrease in mean daily OFF time were assessed using an end-of-treatment analysis [E] - based on the difference in terms of the mean amount of daily time in each state (ie. ON time without troublesome dyskinesia and OFF time) between baseline and endpoint.

Treatment-average analysis [A]: based on the difference between the mean amount of daily time in each state at baseline and the mean amount of daily time in each state over the course of the treatment period (calculated using available diary data from multiple post-baseline time points).

Source: Compiled during the evaluation based on Sections 2.3-2.5 of the submission.

- 6.8 There was inadequate information on a number of design characteristics for the rasagiline studies such as adequate concealment or reporting bias, presumably because the sources of data were solely from publications.
- 6.9 The key outcome measures primarily related to improvements in functionality determined through patient self-assessment and/or clinician assessment using questionnaires and patient diaries.
- 6.10 The net direction of the impact of any bias and confounding arising from heterogeneity across the studies, on the indirect estimates of treatment effect, is difficult to judge. The key factors which raised concerns regarding the transitivity of the studies are summarised as follows:
- Study duration: The duration of treatment varied across the safinamide (24 weeks) and rasagiline (12 to 26 weeks) studies. Different treatment durations are likely to impact indirect estimates of effectiveness and safety;
 - Methods for outcome measurement/analysis varied across studies: As described in Table 3, the method of measuring change in ON time without troublesome dyskinesia varied across the studies ([E]^a versus [A]^b). Thus results cannot be robustly compared unless additional compatible information is provided;
 - The dates and sites of study conduct varied across the included studies: Dates of study conduct varied between 2000/2002 (rasagiline PRESTO and LARGO studies) to 2012 (safinamide SETTLE study) and to 2015/2016 (Hattori). As management of PD is likely to change over time, indirect comparisons between the safinamide and rasagiline studies should be viewed with caution.
 - The placebo effect varied across the included studies, which casts doubt on the comparability of the studies and consequently the validity of the indirect comparison;
 - The dosage/administration of background therapies (both levodopa and other concomitant PD medicines) varied across the included studies, which may impact symptoms of PD and diary based outcomes such as ON and OFF times. The net impact of the differences in baseline/adjunctive therapies on indirect estimates of treatment effect is difficult to judge; and
 - Baseline characteristics such as Unified Parkinson's Disease Rating Scale (UPDRS) Section III (motor examination) and Section II scores (activities of daily living (ADL)) during ON time, varied across the studies. The submission noted that baseline Section II ADL scores during ON time were higher in the safinamide SETTLE and 016 studies (10-12.3) compared to the two rasagiline PRESTO (5.6-6.4) and LARGO (7.3-8.1) studies which reported on this characteristic and that the highest Section III motor examination scores were reported in Study 016 (28.1), followed by the

^a Calculated as the difference between the mean amount of daily ON time without troublesome dyskinesia at baseline and at endpoint.

^b Calculated as the difference between daily ON time without troublesome dyskinesia at baseline and over the course of the treatment period using available diary data from multiple post-baseline time points

CHORAL (24.7), LARGO (23.6), SETTLE (22.3), PRESTO (21.0) and 13484A (18.9) studies. The submission argued that a higher baseline UPDRS Section III score is an independent predictor of a higher placebo response. Any implicit assumption that these differences in Section III scores would overall favour rasagiline over safinamide in an indirect comparison remains speculative. Other transitivity factors that may bias or confound the indirect estimate of effect in potentially any direction would also need to be considered.

- 6.11 The proposed minimal clinically important difference (MCID) was based on the PBAC assessment that 45 minutes was a clinically important difference in the reduction of mean daily OFF time between rasagiline and placebo (Rasagiline July 2011 PSD)^c. The submission argued that a reduction in OFF time represents a decrease in non-functional time whereas an increase in ON time without troublesome dyskinesia represents an increase in time with optimal function. The submission therefore considered it appropriate to propose the same magnitude of change in both parameters as being clinically relevant. An increase in ON time without troublesome dyskinesia is a clinically relevant outcome, although it does not take into account the other multiple non-motor adverse effects of adjunctive therapy. Whether this approach is reasonable is unclear.
- 6.12 The submission also proposed a MCID for both UPDRS Section III motor examination during ON time (2.3 point reduction) and UPDRS Section II activities of daily living during ON time (1.1 point reduction). The MCID for UPDRS Section III was determined from Shulman et al (2010) with some modification applied to the latter for a Section II MCID. The clinical relevance of these MCIDs remains unclear.
- 6.13 The submission used results from 1) pooled analyses of individual patient data (safinamide versus placebo from the 016 and SETTLE studies and a published pooled analysis of the PRESTO and LARGO studies), and 2) meta-analyses of aggregated data (from the 016 and SETTLE safinamide studies and the rasagiline studies) to conduct indirect comparisons between safinamide and rasagiline, using placebo as the common reference.

Comparative effectiveness

- 6.14 The results from the included studies, for the change in 1) mean daily ON time without troublesome dyskinesia, and 2) mean daily OFF time, are summarised below.

^c The submission noted that PBAC made the assessment that a 0.75 hour change in functional status was clinically relevant during consideration of the application to list rasagiline as add-on therapy for fluctuating PD patients receiving levodopa and on the basis of data from the rasagiline LARGO study.

Table 4: Increase in mean daily ON time (hours) without troublesome dyskinesia

Study	Treatment (N)	Baseline		Endpoint		Estimated change	Difference vs placebo (95% CI)
		n	Mean (SD)	n	Mean (SD)	Mean (SE)	
016	placebo	221	9.30 (2.16)	174	10.32 (2.49)	0.72 [∞]	-
	100 mg safinamide	224	9.52 (2.43)	183	11.01 (2.69)	1.28 [∞]	E: 0.55 (0.12, 0.99)
	50 mg safinamide	223	9.37 (2.26)	181	10.88 (2.70)	1.23 [∞]	E: 0.51 (0.07, 0.94)
SETTLE	placebo	275	9.06 (2.50)	275	9.63 (2.77)	0.56 [∞] (0.15)	-
	~90 mg safinamide	274	9.30 (2.41)	274	10.73 (2.75)	1.52 [∞] (0.15)	E: 0.96 (0.56, 1.37)
PRESTO [‡]	placebo	159	9.8 (2.6)	152	-	0.49	-
	1 mg rasagiline	149	9.4 (3.0)	142	-	1.28	A: 0.78 (0.26, 1.31)
LARGO	placebo	229	9.14 (2.97)	218	-	0.03 (0.17)	-
	1 mg rasagiline	231	9.10 (2.91)	222	-	0.85 (0.17)	A: 0.82 (0.36, 1.27) ^β A: 0.81 (0.36, 1.27) [*]
	entacapone	227	9.01 (3.30)	218	-	0.85 (0.17)	A: 0.82 (0.36, 1.27) ^β A: 0.81 (0.36, 1.27) [*]
Zhang	placebo	125	9.50 (2.56)	-	-	0.75 ^μ	-
	1 mg rasagiline	119	9.57 (2.66)	-	-	1.62 ^μ	E: 0.87 (0.43, 1.31) ^μ
Hauser ^{**}	placebo	155	10.2 (SE: 0.2)	151	-	0.4 (0.24) ^α	--
	1 mg rasagiline	154	9.9 (SE: 0.2)	152	-	0.7 (0.24) ^α	E: 0.40 (-0.29, 1.01)
Hattori [‡]	placebo	141	9.64 (NR)	-	-	0.36 [∞] (0.187)	-
	1 mg rasagiline	129	9.60 (NR)	-	-	1.25 [∞] (0.199)	A: 0.90 (0.36, 1.44)

Note: rasagiline studies CHORAL and 13484A did not report data for this outcome measure.

[∞]Least squares mean change.

^βDifference versus placebo as reported in Rascol et al 2005 (p950).

^{*}Difference versus placebo as reported in FDA Clinical Review (p243).

^μZhang reported negative values representing a decrease (or worsening) in the amount of daily ON time. For inclusion in this submission the decreases have been presented as increases or improvements. In addition, Zhang does not specify whether ON time included no, non-troublesome and/or troublesome dyskinesia; it has been assumed to represent ON time without troublesome dyskinesia.

^αMeasured change not adjusted/estimated

[‡]Outcome data for the 0.5 mg/day rasagiline treatment arm of this study were not presented as this strength/dose is not PBS listed.

^{**}The submission did not present outcome data for the preladenant treatment arms of this study as is not PBS listed.

SD = standard deviation; SE = standard error; NR = not reported; CI = confidence intervals; E = End-of-treatment analysis; A = Treatment-average analysis

Source: Table 2.5.1, p111 of the main submission.

Table 5: Decrease in mean daily OFF time, hours

Study	Treatment	Baseline		Endpoint		Estimated change	Estimated difference vs placebo
		n	Mean (SD)	n	Mean (SD)	mean (SE)	(95% CI)
STUDY 016	placebo	221	5.30 (2.06)	214	4.50 (2.66)	-0.70 [∞] (NR)	-
	100 mg safinamide	224	5.20 (2.16)	217	3.90 (2.48)	-1.30 [∞] (NR)	E: -0.6 (-1.0, -0.2)
	50 mg safinamide	223	5.20 (2.08)	215	3.90 (2.58)	-1.30 [∞] (NR)	E: -0.6 (-0.9, -0.2)
SETTLE	placebo	275	5.38 (2.01)	275	4.84 (2.59)	-0.62 [∞] (0.14)	-
	~90 mg safinamide	274	5.34 (1.97)	274	3.77 (2.56)	-1.65 [∞] (0.14)	E: -1.03 (-1.40, -0.67)
PRESTO [‡]	placebo	159	6.0 (2.20)	152	-	-0.91 (NR)	-
	1 mg rasagiline	149	6.30 (2.60)	142	-	-1.85 (NR)	A: -0.94 (-1.36, -0.51) E: -0.89 (-1.55, -0.23)
LARGO	placebo	229	5.55 (2.44)	218	-	-0.40 (0.15) E -0.59	-
	1 mg rasagiline	231	5.58 (2.37)	222	-	-1.18 (0.15) E -1.13	A: -0.78 (-1.18, -0.39) E: -0.54 (-1.04, -0.05)
	entacapone	227	5.60 (2.59)	218	-	-1.20 (0.15) E -1.29	A: -0.80 (-1.20, -0.41) E: -0.70 (-1.19, -0.21)
Zhang	placebo	125	6.26 (2.46)	-	-	-0.69 ^{**}	
	1 mg rasagiline	119	6.28 (2.37)	-	-	-1.75 ^{**}	E: -1.06 (-1.44, -0.68) ^{**}
Hauser [‡]	placebo	155	5.70 (SE: 0.2)	151	-	-0.82 (0.21)	-
	1 mg rasagiline	154	5.60 (SE: 0.2)	152	-	-1.12 [*] (0.21)	E: -0.30 (-0.90, 0.26)
Hattori ^{***}	placebo	141	6.05 (2.28)	138	-	-0.51 [∞] (0.17)	-
	1 mg rasagiline	129	6.12 (2.43)	122	-	-1.35 [∞] (0.18) -1.40 [∞] (0.22)	A: -0.84 (-1.32, -0.36) E: -0.90 (-1.49, -0.30)
CHORAL	placebo	158	6.13 (2.72)	150	-	-0.76 [*] (0.16)	-
	1 mg rasagiline	163	6.10 (2.60)	158	-	-1.25 [*] (0.16)	A: -0.50 (-0.92, -0.07)
13484A	placebo	66	6.24 (2.73)	59	-	-1.24 [*] (0.26)	-
	1 mg rasagiline	66	6.26 (2.29)	63	-	-1.59 [*] (0.25)	A: -0.35 (-0.93, 0.23) [‡]

SD = standard deviation; SE = standard error; CI = confidence intervals; E = End-of-treatment analysis; A = Treatment-average analysis; NR = not reported in main submission.

[∞] Least squares mean change.

^{*}Actual not adjusted/estimated change.

^{**}Zhang reports positive values representing an increase (or worsening) in the amount of daily OFF time. For inclusion in this submission the increases have been presented as decreases or improvements.

[‡]90% Confidence interval

^{***}Outcome data for the 0.5 mg/day rasagiline treatment arm of this study are not presented as this strength/dose is not PBS listed.

[‡]Outcome data for the 0.5 mg/day rasagiline treatment arm of this study were not presented as this strength/dose is not PBS listed

[‡]Outcome data for the praladenant treatment arms of this study are not presented as this active ingredient is not PBS listed.

Source: Table 2.5.2, p113 of the main submission.

6.15 In Study 016, based on the submission's proposed MCID of ≥ 0.75 hours (≥ 45 minutes), the point estimate of the increase in mean daily ON time without troublesome dyskinesia, was statistically significant, but not clinically meaningful, for both safinamide treatment arms (100 mg /day arm (difference of 0.55 hours vs. placebo) and 50 mg/day arm (difference of 0.51 hours vs. placebo)). Notably, the benefit over placebo was quite similar between the low and high fixed doses of safinamide. The long term data (78 week extension period) observed from Study 018 did not change these observations, apart from the outcome of increase in mean daily ON time without troublesome dyskinesia associated with the 100 mg/day safinamide arm compared with placebo (difference of 0.83 hours vs. placebo).

- 6.16 In the SETTLE study, based on the submission’s proposed MCID of ≥ 0.75 hours, the point estimate of the increase in mean daily ON time without troublesome dyskinesia and the decrease in mean daily OFF time associated with the safinamide treatment arm (50 mg/day titrated after two weeks to 100 mg daily) over placebo, was statistically significant and clinically important. The magnitude of this increase (ON time) and decrease (OFF time) from baseline to Week 24, that was attributable to safinamide, was approximately one hour.
- 6.17 Except for the Hauser study, the point estimates of the change in mean daily ON time without troublesome dyskinesia and reduction in OFF time, associated with rasagiline 1 mg/day over placebo, were statistically significant and clinically important.
- 6.18 Both safinamide and rasagiline reduced UPDRS sections III (motor) and II (ADL) scores from baseline compared with the corresponding placebo arms of the individual studies.
- 6.19 The submission presented numerous indirect comparisons using different statistical methods (pooled individual patient data (IPD) and meta-analyses of aggregate data), and efficacy data derived from different measurement methods (either E, A or E+A analysis). Some analyses were considered “primary” and some as “sensitivity” analyses by the submission. Given the extent of the transitivity issues, these analyses are at best exploratory.
- 6.20 The results of the indirect comparison are summarised below. The indirect comparisons included both pooled analyses of individual patient data (IPD) and meta-analyses of aggregated data. There was substantial heterogeneity across the studies and the results of the indirect comparisons should be interpreted in this context.

Table 6: Indirect comparisons of the increases in mean daily ON time (hours) without troublesome dyskinesia between safinamide 100 mg/day and rasagiline 1 mg/day treatments (pooled analyses of individual patient data (IPD) and meta-analyses of aggregated data).

Basis of comparison		Treatment effect vs placebo Effect size (95% CI) (hours)		Safinamide vs rasagiline Effect size (95% CI) (hours)
Safinamide 100 mg/day	Rasagiline 1 mg/day	Safinamide 100 mg/day	Rasagiline 1 mg/day	
Primary indirect comparisons in the submission - 016 + SETTLE vs Hauser, PRESTO, LARGO, and Hattori				
Pooled IPD analysis	Primary meta-analysis	0.85 (0.54, 1.16)	0.76 (0.49, 1.02)	0.09 (-0.32, 0.50)
Meta-analysis	Primary meta-analysis	0.76 (0.36, 1.16)	0.76 (0.49, 1.02)	0.004 (-0.48, 0.49)
Sensitivity indirect comparisons in the submission – 016 + SETTLE vs LARGO + PRESTO				
Pooled IPD analysis	Pooled IPD analysis	0.85 (0.54, 1.16)	0.73 (0.37, 1.08)**	0.12 (-0.35, 0.59)
Meta-analysis	Sensitivity meta-analysis	0.76 (0.36, 1.16)	0.80 (0.46, 1.15)	-0.04 (-0.57, 0.49)
Sensitivity indirect comparisons – “most favourable” to rasagiline: 016 + SETTLE vs LARGO, PRESTO and Hattori				
Pooled IPD analysis	Sensitivity meta-analysis	0.85 (0.54, 1.16)	0.83 (0.54, 1.12)	0.02 (-0.41, 0.44)
Meta-analysis	Sensitivity meta-analysis	0.76 (0.36, 1.16)	0.83 (0.54, 1.12)	-0.07 (-0.56, 0.43)

**The submission *reasonably* noted that the estimated difference reported for the pooled PRESTO/LARGO data is lower than would be expected from the outcomes reported in the individual trials: 0.78 (0.26, 1.31) and 0.82 (0.36, 1.27), respectively, and thus the results should be interpreted with caution.

Source: Table 2.6.15, p142 of the main submission.

Table 7: Indirect comparisons of the increases in mean daily ON time (hours) without troublesome dyskinesia between safinamide 50 mg/day and rasagiline 1 mg/day treatments (pooled analyses of individual patient data (IPD) and meta-analyses of aggregated data).

Basis of comparison		Treatment effect vs placebo Effect size (95% CI) (hours)		Safinamide vs rasagiline Effect size (95% CI) (hours)
Safinamide 50 mg/day	Rasagiline 1 mg/day	Safinamide 50 mg/day	Rasagiline 1 mg/day	
Primary indirect comparisons in the submission - 016 + SETTLE vs Hauser, PRESTO, LARGO, and Hattori				
Pooled IPD analysis	Primary meta-analysis	0.50 (0.08, 0.91)	0.76 (0.49, 1.02)	-0.26 (-0.75, 0.23)
Sensitivity indirect comparisons: 016 + SETTLE vs LARGO + PRESTO				
Pooled IPD analysis	Pooled IPD analysis	0.50 (0.08, 0.91)	0.73 (0.37, 1.08)	-0.23 (-0.78, 0.32)
Sensitivity indirect comparisons – most favourable to rasagiline: 016 + SETTLE vs LARGO, PRESTO and Hattori				
Pooled IPD analysis	Sensitivity meta-analysis	0.50 (0.08, 0.91)	0.83 (0.54, 1.12)	-0.33 (-0.84, 0.18)

Source: Table 2.6.16, p142 of the main submission.

- 6.21 The indirect analyses indicated that there were no statistically significant or clinically important differences between safinamide 100 mg/day and rasagiline 1 mg/day in terms of increasing ON time without troublesome dyskinesia, with the 95% confidence intervals excluding a difference of 0.75 hours (the proposed MCID or non-inferiority margin). Safinamide 100 mg/day appeared to be non-inferior to rasagiline 1 mg/day. The interpretation of these results should consider that the outcome data for safinamide “100 mg/day” represents pooled individual patient and meta-analysed data from both the fixed 100 mg/day safinamide arm of 016 and the 50 mg/day starting dose up-titrated to 100 mg/day after two weeks arm of SETTLE. The treatment effect associated with these safinamide dosing regimens differed between the two trials with the larger effect observed in SETTLE.
- 6.22 No meta-analyses were performed for the safinamide 50 mg dose. Comparisons were based on the pooled analysis of IPD which primarily reflected the 50 mg/day arm of Study 016. The indirect comparisons for change in mean daily ON time without troublesome dyskinesia indicated a difference of 0.26 hours (15.5 minutes) in favour of rasagiline 1 mg/day. The 95% CIs did not exclude a clinically important difference greater than 0.75 hours and thus the condition for non-inferiority was not met. The results appeared consistent across “primary” and “sensitivity” analyses. If a final TGA approved PI for safinamide subsequently recommends that patients titrate upwards from 50 mg/day to 100 mg/day, these results may not be relevant.
- 6.23 There were no statistically significant or clinically important differences between safinamide 100 mg/day and rasagiline 1 mg/day in terms of change in OFF time. The 95% confidence intervals excluded a difference of 0.75 hours (the proposed MCID). Safinamide 100 mg/day is therefore non-inferior to rasagiline 1 mg/day in terms of decreasing OFF time. As was the case for the outcome of increase in ON time without troublesome dyskinesia, decrease in OFF time for “100 mg/day” safinamide represents pooled individual patient and meta-analysed data from both the fixed 100 mg/day safinamide arm of 016 and the 50 mg/day starting dose up-titrated to 100

mg/day after two weeks arm of SETTLE. The results were similar for the indirect comparisons between safinamide 50 mg/day and rasagiline 1 mg/day.

- 6.24 There were no statistically significant or clinically important differences between safinamide 100 mg/day and rasagiline 1 mg/day in terms of the change in UPDRS Section III although the estimated effect sizes across the “primary” and “sensitivity” indirect comparisons ranged between 0.11 and 0.79 points in favour of rasagiline. However, the 95% confidence intervals excluded a difference of 2.3 points (the proposed MCID) and thus safinamide 100 mg/ day appeared to be non-inferior to rasagiline 1 mg/day.
- 6.25 For the indirect comparison between safinamide 50 mg/day and rasagiline 1 mg/day in terms of the change in UPDRS Section III, there was a non-statistically significant difference of 1.21 points in favour of rasagiline. The 95% CI did not exclude the proposed MCID of greater than 2.3 points and thus the basis for non-inferiority was not met.
- 6.26 The reduction from baseline in UPDRS Section II (during ON time) was statistically significantly greater for safinamide 100 mg/day compared to rasagiline 1 mg/day. The 95% confidence intervals excluded a difference of 1.1 points (the proposed MCID). Safinamide 100 mg/day therefore appeared to be non-inferior to rasagiline 1 mg/day. Similar results were observed for 50mg/day safinamide compared with rasagiline.

Comparative harms

- 6.27 The proportion of patients experiencing adverse events (AEs) between the MAO-B vs. placebo arms of the included studies did not vary substantially except for the Hattori (73.6% vs 50.4%) and 13484A (28.9% vs 18.2%) rasagiline studies. However, there was substantial variability in the incidence of AEs across the trials. Among the rasagiline studies, the placebo AE rate ranged from 8% in CHORAL to 87% in PRESTO with a similar pattern for the corresponding MAO-B inhibitor arms.
- 6.28 Dyskinesia was the most commonly reported AE in all trials, except for the rasagiline Zhang study where the frequency was low (<1%). The incidence was higher in the MAO-B inhibitor arms than in the placebo arms for all studies except CHORAL and Zhang.
- 6.29 The results of indirect comparison of any AE, discontinuation due to an AE, serious AEs (SAEs) and deaths between 100 mg/day safinamide and rasagiline 1mg/day are summarised below.

Table 8: Indirect comparisons of safety - Safinamide 100 mg/day versus rasagiline 1 mg/day (meta-analyses of aggregated data)

Basis of comparison (included studies)		Treatment effect vs placebo Effect size (95% CI) (hours)		Safinamide vs rasagiline Effect size (95% CI) (hours)
Safinamide 100 mg/day (016 and SETTLE)	Rasagiline 1 mg/day (PRESTO, LARGO, Hauser, Hattori, CHORAL, 13484A, Zhang)	Safinamide 100 mg/day	Rasagiline 1 mg/day	
Any adverse event				
Meta-analysis RR	Meta-analysis RR	0.97 (0.89, 1.09)	1.14 (0.99, 1.29)	0.85 (0.73, 1.00)
Meta-analysis RD	Meta-analysis RD	-0.02 (-0.08, 0.04)	0.06 (0.002, 0.12)	-0.08 (-0.16, 0.00)
Discontinuations due to adverse events				
Meta-analysis RR	Meta-analysis RR	1.45 (0.86, 2.46)	1.33 (0.92, 1.93)	1.09 (0.57, 2.08)
Meta-analysis RD	Meta-analysis RD	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.04)	0.00 (-0.20, 0.21)
Serious adverse events				
Meta-analysis RR	Meta-analysis RR	0.91 (0.53, 1.57)	1.23 (0.86, 1.78)	0.74 (0.38, 1.43)
Meta-analysis RD	Meta-analysis RD	-0.01 (-0.05, 0.04)	0.01 (-0.01, 0.02)	-0.02 (-0.06, 0.03)
Deaths				
Meta-analysis RR	Meta-analysis RR	1.43 (0.32, 6.33)	0.71 (0.21, 2.40)	2.01 (0.30, 13.69)
Meta-analysis RD	Meta-analysis RD	0.003 (-0.02, 0.02)	-0.001 (-0.01, 0.01)	0.00 (-0.02, 0.02)

RR = Relative Risk; RD = Risk Difference; AE = Adverse event; SAE = serious adverse event.

Results in terms of odd ratios can be found in the submission.

Source: Table 2.6.23, p146 of the main submission.

- 6.30 There were no statistically significant differences between the treatments in discontinuations due to AEs, SAEs or deaths. The submission concluded that safinamide 100 mg/day was non-inferior to rasagiline 1 mg/day in terms of safety. The ESC considered that the AE profile of safinamide and rasagiline appeared similar, based on the indirect comparison and safety is likely to be similar as rasagiline is a pharmacological analogue of safinamide.
- 6.31 Results for the indirect comparisons of safety between 50 mg/day safinamide and 1mg/day rasagiline were not statistically significant except for SAEs which favoured safinamide 50 mg/day over rasagiline 1mg/day (RR=0.36; 95% CI: 0.15, 0.87). However, the submission concluded that safinamide 50 mg/day was non-inferior to rasagiline 1 mg/day in terms of safety. The ESC considered that this was appropriate but noted that it appears that the 50 mg dose of safinamide is associated with fewer adverse events than the 100 mg dose.
- 6.32 A cautious interpretation of the indirect comparisons of safety is required given some differences in treatment durations, adjunctive therapies and patients/disease characteristics across the studies.

Clinical claim

- 6.33 The submission described safinamide as non-inferior to rasagiline in terms of efficacy and safety.
- 6.34 The submission's clinical claim should be viewed within the context of concerning heterogeneity among the safinamide and rasagiline studies that may distort indirect

estimates of treatment effect, albeit in an unclear direction, as discussed above. There were differences across the studies in terms of periods of study conduct, treatment durations; baseline levodopa and adjunctive therapies, baseline disease characteristics and measurement methods for diary based outcomes. There are also applicability issues regarding the proposed dosing of safinamide and the safinamide dosing in the key 016 and SETTLE studies. The ESC noted that the comparison was limited by the lack of head to head trials available and the substantial heterogeneity in the studies included in the indirect comparison.

6.35 Overall, within the limitations of the available data, the evaluator cautiously made the following conclusions regarding the comparative efficacy and safety of safinamide compared with rasagiline, as add-on therapy to a stable dose of levodopa regimen, in mid-to-late stage fluctuating PD:

- Safinamide (regardless of dose) appears to be non-inferior to rasagiline 1 mg/day in terms of safety;
- Starting therapy with safinamide 50 mg/day and up-titrating to 100 mg/day after two weeks (where tolerability permits), seems to be non-inferior to rasagiline 1 mg/day. The indirect comparison results suggested non-inferiority for the 100 mg dose of safinamide for all outcomes (changes in ON and OFF times and UPDRS scores). However, the clinical benefit observed in the fixed 100 mg/day safinamide treatment arm of Study 016 was not as convincing as that observed in SETTLE. Moreover, starting with a fixed safinamide 100 mg/day dose, as in Study 016, is not a recommended or proposed regimen making the applicability of the corresponding efficacy data limited. The ESC considered that within the limitations of the available data the claim of non-inferiority of the 100 mg/day dose of safinamide to rasagiline 1 mg/day appears reasonable.
- Results of the indirect comparisons between safinamide 50 mg/day and rasagiline 1 mg/day did not exclude the possibility that this dose of safinamide may be inferior to rasagiline. There appeared to be a trend favouring rasagiline 1 mg/day although there was a lack of statistical significance likely arising from a lack of precision in some of the analyses. Based on the proposed MCIDs in the submission, non-inferiority was not demonstrated for a fixed 50 mg/day dose of safinamide to rasagiline 1 mg/day in terms of the increase in ON time without troublesome dyskinesia and improvement in UPDRS section III motor examination scores. The ESC considered that the ability to use the 50 mg/day dose of safinamide is likely to have utility for some patients, noting that the equi-effective dose calculations are appropriately based on the 100 mg/day dose.

6.36 The PBAC considered that the claim of non-inferior comparative effectiveness for the steady state 100 mg/day dose of safinamide, following titration from 50 mg/day where tolerated, compared with 1 mg/day of rasagiline, was reasonable. The PBAC considered that the claim of non-inferior comparative effectiveness for the steady state 50 mg/day dose of safinamide compared with 1 mg/day of rasagiline was not adequately supported by the data.

6.37 The PBAC considered that the claim of non-inferior comparative safety was reasonable for both the 50 mg/day and 100 mg/day doses of safinamide compared with rasagiline.

Economic analysis

6.38 The equi-effective doses were estimated as safinamide 100 mg daily and 1mg rasagiline daily.

6.39 The submission justified these equi-effective doses on the following basis:

- Rasagiline 1 mg is the only dose of this medicine listed on the PBS. All rasagiline clinical trials presented in the submission included a rasagiline 1 mg/day treatment arm;
- The equi-effective dose for safinamide was based on the therapeutic conclusion that safinamide 100 mg/day is non-inferior to rasagiline 1 mg/day in terms of both efficacy and safety.

6.40 As stated above, starting therapy with safinamide 50 mg/day and up-titrating to 100 mg/day after two weeks (where tolerability permits), is non-inferior to rasagiline 1 mg/day. According to the PBAC Guidelines, steady state doses should be used in the cost-minimisation analysis, therefore it is appropriate to use 100 mg safinamide compared to 1mg rasagiline. This is consistent with the recommended dosage in the approved PI. The ESC agreed that it was appropriate to consider 100 mg of safinamide and 1 mg of rasagiline as the equi-effective doses.

6.41 The submission used the price of rasagiline prior to the 5% statutory price reduction that occurred on 1 April 2018 in the context of clause 5.7 of the 2017 Strategic Agreement between Medicines Australia and the Commonwealth. The ESC noted that this is a matter for the Minister (or delegate).

6.42 The submission proposed that the cost for the 50 mg strength pack would be █% of the price of the 100 mg strength pack.

Drug cost/patient/year: \$ █

6.43 This is based on the DPMQ of \$ █ for a 100 mg pack of safinamide (30 tablets), which is sufficient for a 30 day supply. This is compared to a cost of \$1,347 for rasagiline, based on the DPMQ of \$110.70 for one pack (30 tablets) for a 30 day supply. It is noted that the cost of safinamide is based on an assumption that all patients will be treated with 100 mg safinamide. The approved PI recommends that treatment should be started at 50 mg/day and the dose may be increased to 100 mg/day after two weeks on the basis of individual clinical need, therefore it is likely that some patients will remain on the 50 mg dose.

Estimated PBS usage & financial implications

6.44 This submission was not considered by DUSC.

- 6.45 The submission used a market share approach to estimate the likely uptake and financial implications associated with listing safinamide on the PBS as a once-daily add-on therapy to levodopa in patients with Parkinson’s disease and motor fluctuations.
- 6.46 The submission assumed that the proportion of 50 mg safinamide scripts was █%, █% and █% in the first three years of listing (respectively), and equalled █% in years 4-6. The approved PI of safinamide is pending and therefore the doses of safinamide, and consequently the relative usage of 50mg pack or 100mg pack in clinical practice is uncertain. Although data from other countries indicated that the usage of 100mg safinamide was much lower than that predicted in the submission, the international experience in the use of safinamide is still limited given the relatively new availability of safinamide and long term data of safinamide usage is lacking. The ESC considered that the uptake of safinamide is uncertain, as is the proportion of patients that would remain on the lower 50 mg dose.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total services (packs) of safinamide						
Safinamide 50 mg packs	█	█	█	█	█	█
Safinamide 100 mg packs	█	█	█	█	█	█
Total packs	█	█	█	█	█	█
Estimated financial implications of safinamide						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Less co-payments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for rasagiline						
Cost to PBS/RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Reduction in cost to PBS/RPBS less copayments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net financial implications						
Net cost to PBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to the PBS/RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

Source: Compiled during the evaluation based on information presented in '3A.1. Safinamide utilisation and cost workbook.xlsx'

The redacted table shows that at year 6, the estimated number of packs was 10,000 – 50,000 per year.

- 6.47 The submission estimated a modest cost-saving associated with listing safinamide on the PBS. This is primarily due to the usage of the less expensive 50 mg packs of safinamide (priced at █% of the cost of the 100 mg strength). As noted above, the extent of usage of 50 mg pack of safinamide is uncertain. The ESC noted that the cost-saving comes from patients staying on the 50 mg dose (█% of the cost of the 100 mg tablet).
- 6.48 At year 5, the estimated net reduction in cost to the PBS from listing safinamide would be less than \$10 million dollars per year. The PSCR (p4) stated that using a range of plausible inputs the financial impact remained cost-saving. The ESC considered that

the cost saving as presented in the submission resulting from listing of safinamide may not be realised because:

- there is a population of patients that cannot tolerate rasagiline, who may be treated with safinamide, resulting in an increase in the overall market size; and
- the proportion of patients remaining on the 50 mg dose is uncertain. A smaller proportion of patients on the 50 mg dose would result in a smaller cost-saving. In the SETTLE study, where patients were up-titrated to 100 mg/day if tolerated, only 1.8% of patients remained on the 50 mg/day safinamide dose.

Quality Use of Medicines

6.49 A fixed dose of 50 mg/day safinamide did not demonstrate non-inferiority to 1 mg/day rasagiline. The QUM issue raised is whether a finalised dosing regimen for safinamide would ensure that patients receive an adequate dose. The PSCR (p1) considered that a proportion of patients would derive adequate therapeutic benefit from 50mg/day.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of safinamide on the General Schedule as a Restricted Benefit listing for treatment of Parkinson's disease (PD), as add-on therapy to levodopa, on the basis of cost-minimisation compared to rasagiline. The equi-effective doses are safinamide 100 mg/day and rasagiline 1 mg/day.

7.2 The PBAC noted that the terms mid-to-late stage disease and requirement for a stable dose of levodopa were excluded from the TGA indication and the final indication is for the treatment of adult patients with fluctuating idiopathic Parkinson's disease as add-on therapy to a regimen that includes levodopa. The PBAC agreed that the restriction should be consistent with the TGA indication and considered that it would be appropriate to exclude from the restrictions criteria for disease stage, stable levodopa dose and motor fluctuations as advised by the ESC.

7.3 The PBAC accepted rasagiline as the appropriate comparator for safinamide. The PBAC noted that selegiline is listed on the PBS for use in a subset of the requested population for safinamide (late stage Parkinson's Disease) and was the main comparator in the cost-minimisation recommendation of rasagiline. However the PBAC considered that selegiline was not the relevant main comparator, on the basis of its worse safety profile and thus limited use. The PBAC noted that selegiline is used infrequently due the lower selectivity for MAO-B over MAO-A (particularly at high doses) compared to rasagiline and potential cardiac and psychiatric effects. The PBAC noted that the side effects of selegiline's amphetamine and methamphetamine metabolites may be of benefit in a discreet subgroup of patients who suffer from daytime somnolence as a comorbidity and considered that this may account for its continuing use in a small number of patients, which would be unlikely to be replaced by safinamide.

7.4 The PBAC noted that the evidence presented was an indirect comparison of two RCTs

of safinamide versus placebo and seven RCTs of rasagiline versus placebo of various trial durations. The PBAC noted that there were substantial limitations in the indirect comparison due to transitivity issues in terms of periods of study conduct, treatment durations; baseline levodopa and adjunctive therapies, baseline disease characteristics and measurement methods for diary based outcomes and applicability issues regarding the proposed dosing of safinamide and the safinamide dosing in the key 016 and SETTLE studies.

- 7.5 Notwithstanding the limitations in the indirect comparison the PBAC was satisfied that safinamide 100 mg/day appears to be non-inferior to rasagiline 1 mg/day in comparative effectiveness. The PBAC considered that the claim of non-inferior comparative effectiveness for the 50 mg/day dose of safinamide compared with 1 mg/day of rasagiline was not adequately supported by the data, but acknowledged that 50 mg may provide a suitable therapeutic option in some patients who are unable to up-titrate to 100 mg daily. The PBAC however noted that the proportion of patients who should remain on the 50 mg/day dose due to tolerability would be very low, in the region of 10% or less, noting that in the SETTLE study, where patients were up-titrated to 100 mg/day if tolerated, only 1.8% of patients remained on the 50 mg/day safinamide dose.
- 7.6 The PBAC was further of the view that as the 50 mg/day form would be predominantly used for titration when patients commence therapy and was not therapeutically equivalent to the 100 mg/day, it may be more appropriate for a price per mg for the 50 mg/day form that is the same as the price per mg for the 100 mg/day form.
- 7.7 The PBAC noted that there were no statistically significant differences between safinamide 100 mg/day and rasagiline 1 mg/day in discontinuations due to adverse events, serious adverse events or deaths. The PBAC considered that the claim of non-inferior safety for safinamide 100 mg/day compared with rasagiline 1 mg/day appears reasonable. The PBAC noted that the results for the indirect comparisons of safety between 50 mg/day safinamide and 1mg/day rasagiline were not statistically significant except for serious adverse events which favoured safinamide 50 mg/day over rasagiline 1mg/day (RR=0.36; 95% CI: 0.15, 0.87). However, the PBAC considered that the claim of non-inferior safety to rasagiline 1 mg/day appears reasonable.
- 7.8 The PBAC noted the sponsor's request for the price of safinamide to be based on the price of rasagiline prior to the 5% statutory price reduction that occurred on 1 April 2018, in the context of clause 5.7 of the 2017 Strategic Agreement between Medicines Australia and the Commonwealth. The PBAC noted that this is a matter for the Minister (or delegate).
- 7.9 The PBAC considered that the estimated financial impact associated with listing safinamide on the PBS was uncertain due to uncertainty in the split between the 50 mg and 100 mg doses used in practice. The PBAC noted that the minor expected cost saving associated with the use of the less costly 50 mg dose was also highly uncertain.
- 7.10 The PBAC considered that safinamide was suitable for prescribing by nurse practitioners.

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- 7.11 The PBAC recommended that safinamide should be treated as interchangeable on an individual patient basis with rasagiline.
- 7.12 The PBAC recommended that the Early Supply Rule should apply.
- 7.13 The PBAC noted that this submission does not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Proprietary Name and Manufacturer	
SAFINAMIDE				
50 mg tablet	30	5	Xadago™	Seqirus
100 mg tablet	30	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Parkinson Disease
PBS Indication:	Parkinson Disease
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be as adjunctive therapy to a levodopa-decarboxylase inhibitor combination.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

9 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.

10 Sponsor's Comment

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The Sponsor welcomes the PBAC's decision to recommend safinamide, that will provide an alternative add-on therapy for the management of fluctuating Parkinson's disease patients being treated with levodopa.