Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rasagiline

Proprietary Product Name: Azilect

Sponsor: Lundbeck Australia Pty Ltd

February 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	12 September 2011
Active ingredient(s):	Rasagiline (as mesilate)
Product Name(s):	Azilect
Sponsor's Name and Address:	Lundbeck Australia Pty Ltd PO Box 1973, Macquarie Centre, NSW, 2153
Dose form(s):	Tablet
Strength(s):	1 mg (expressed in terms of rasagiline free base)
Container(s):	Blister packs or Plastic bottles
Pack size(s):	10& 30 tablets/blister pack or 30 tablets/bottle
Approved Therapeutic use:	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.
Route(s) of administration:	Oral
Dosage:	1 mg/day
ARTG Number (s)	AUST R 170172 (blister pack), AUST R 172457 (bottle)

Product Background

Parkinson's Disease (PD) is a neurodegenerative disorder characterised by a loss of dopaminergic neurons in the substantia nigra. The current first line pharmacological treatment for PD is the dopamine precursor, levodopa. Less common approaches are dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase (MAO) inhibitors.

MAO is classified into two major molecular species, A and B, and is localized in mitochondrial membranes throughout the body in neurons and other cells of the nervous system, liver, gastrointestinal tract and many other tissues. MAO regulates the metabolic degradation of catecholamines and serotonin in the central nervous system (CNS) and peripheral tissues. MAO-B is found primarily in glial cells and is the major form in the human brain.

In *ex vivo* animal studies in brain, liver and intestinal tissues, rasagiline has been shown to act as an inhibitor of MAO-B. The precise mechanism(s) of action of rasagiline is however unknown. One mechanism is believed to be related to its MAO-B inhibitory activity which causes an increase in extracellular levels of dopamine in the central nervous system (CNS; striatum). The elevated dopamine level and subsequent increased dopaminergic activity may mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

Rasagiline was first evaluated by the TGA in 2004. That application was eventually rejected by the TGA Delegate, primarily on the grounds of an apparent risk of melanoma in patients taking rasagiline. The sponsor lodged an appeal against the decision but the decision was upheld. The

sponsor then lodged an appeal in the Administrative Appeals Tribunal but during pre-hearing negotiations it became evident that relevant new data had become available. This new information, including an additional clinical study and evidence from published papers, is presented in the current Australian submission.

This AusPAR describes the application by Lundbeck Australia Pty Ltd to register Azilect, a 1 mg tablet of rasagiline as mesilate, 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).*

Regulatory Status

The current overseas regulatory status of this product is summarised in Table 1 below.

Table 1. Selected Overseas regulatory status of Azilect.

Country	Name	Approval date
EU Centralised procedure MAA renewal	Azilect 1 mg tablets Azilect	21 February 2005 21 September 2009
USA	Azilect 0.5 mg tablet 1 mg tablet	16 May 2006
Switzerland	Azilect 1 mg tablet	20 December 2005
Canada	Agilect 0.5 mg tablet 1mg tablet	17 August 2006

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

This application is a resubmission. Lundbeck originally applied to register Azilect (rasagiline) 1 mg tablets in March 2004. The application was rejected in December 2005 on safety grounds. At that time, there were no objections to registration of the product with regard to Chemistry, Manufacturing and Controls.

The specifications have been updated to include a limit for each of four potentially genotoxic impurities. The higher limit applied to a mutagenic impurity has been cleared by the Nonclinical Section at TGA. The limit for total impurities has also been tightened.

An additional site of manufacture of the finished product has been nominated in the present application. Manufacture of the tablets at both sites has been satisfactorily validated.

Updated stability data have been provided to support a shelf life of 3 years below 25°C for the tablets in both the blister packs and the bottles.

No new bioavailability data were submitted with the present application. Previously submitted data showed that the absolute bioavailability of rasagiline tablets is 36% and that the principal metabolite, 1-aminoindan, has a higher plasma exposure (area under the plasma concentration time curve (AUC)) after oral administration of rasagiline tablets than after intravenous (IV) administration of rasagiline. In fact, the sum of the mean rasagiline and 1-aminoindan area under the plasma concentration time curve from time zero to infinity (AUC_{∞}) values on a molar basis is 299 pmol.h/mL after oral administration and 292 pmol.h/mL after IV administration, indicating that the drug is completely absorbed after oral administration. Its absolute oral bioavailability is therefore limited by a high first pass effect.

Another study submitted and evaluated with the previous Australian application showed that a high fat meal reduces the AUC and C_{max} of rasagiline by about 20% and 60%, respectively, but has no significant effect on the AUC or maximal plasma concentration (C_{max}) of 1-aminoindan. The clinical evaluator of the previous application objected to the statement in the PI that the AUC is not significantly affected by food but the statement remains in the PI submitted with the present application. This has been brought to the attention of the current Clinical Delegate.

There are no objections to registration of this product in respect of Chemistry, Manufacturing and Controls.

III. Nonclinical Findings

Introduction

Two newly submitted nonclinical studies were evaluated with this application: an *in vitro* pharmacology study and an embryofetal developmental toxicity study of rasagiline mesilate in rabbits. In addition, the sponsor has submitted more than 60 published papers based on a literature search conducted in 2009. The most relevant articles were received in response to a TGA request. The literature search was restricted to articles published from 2003 onwards. A Nonclinical Expert Statement was submitted by the sponsor in lieu of a Nonclinical Overview and Summaries.

A comprehensive nonclinical package was submitted with the original application. A further three analytical development studies were received in response to a request from TGA.

One published literature reference provided further evidence of reduced monoamine oxidase type-B (MAO-B) activity following treatment with rasagiline, as well as enhanced L-DOPA[1] – induced effects (intensity and duration of contralateral turning) in guinea pigs. It is noted that an advantage of this model is that guinea pigs have a greater proportion of MAO-B (compared to MAO-A) than rats.

The other submitted literature references concerned with the pharmacology of rasagiline mainly comprised studies addressing the neuroprotective effect of this compound. This was discussed in some detail in the previous, original nonclinical evaluation report and there were no findings that had any significant impact on the assessment of primary pharmacology of rasagiline, except that more evidence was provided to show that the primary metabolite of rasagiline, aminoindan, also had neuroprotective activity.

The pharmacology study currently submitted by the sponsor showed no inhibition of the potassium tail current (from hERG channels expressed in HEK293 cells) at 1 µg/mL (>100x the

[1] L-DOPA=L-3,4-dihydroxyphenylalanine. L-DOPA is the precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) collectively known as catecholamines.

mean Cmax in patients at the recommended clinical dose). None of the previously submitted studies investigated the effects of rasagiline mesilate on the hERG current.

A few of the submitted literature references also addressed the cardiovascular safety pharmacology of rasagiline. In anaesthetised Sprague Dawley rats, treatment with rasagiline resulted in reduced mean arterial pressure (MAP) following a bolus IV dose of 10 mg/kg but not after a 1 mg/kg dose. After repeated oral (PO) dosing at 1 mg/kg/day for up to 21 days, MAP as well as systolic and diastolic blood pressure tended to be significantly reduced but were not affected in another study with the same dosing regimen using conscious SD rats. The potential for blood pressure reduction was noted in the previous nonclinical evaluation report. No significant effect on heart rate (HR) was detected in these studies. Neither blood pressure, HR nor catecholamine release was affected by rasagiline in pithed rats.

In conscious New Zealand White (NZW) rabbits significant increases (8%) in the QT and QTc intervals[2] relative to baseline were seen after 1 mg rasagiline. However, there was no significant difference when compared to vehicle treated animals and the findings were considered to be of equivocal toxicological significance.

Overall, the findings from the currently submitted studies do not significantly alter the risk profile for cardiovascular parameters in comparison with the findings from previously submitted studies.

Pharmacology

No new data were submitted under this heading.

Pharmacokinetics

No new data were submitted under this heading.

Toxicology

Carcinogenicity

The clinical trial data have suggested a possible association between rasagiline treatment and melanoma. The findings of the SD rat carcinogenicity study submitted previously with the original application were negative, with plasma exposures (AUC) reaching ≥80 fold the clinical exposure, although one high dose male rat was found to have malignant melanoma of the pinna (1/130 rats = 0.77%). This was also noted in the FDA evaluation report for rasagiline. Amelanotic melanomas are very uncommon in albino animals (incidences are variously reported as 0.06% - 0.6% from several studies), and pigmented animals may have been a more appropriate model to assess the potential for rasagiline to induce melanomas. A single incidence of this rare tumour type in one animal of one of the albino species tested is not readily interpreted, therefore the potential for the compound to induce this tumour type has not been adequately assessed. In the original CD-1 mouse carcinogenicity assay, rasagiline treatment at high doses was associated with increased incidences of lung tumours (combined adenoma/carcinoma); the no-effect dose (1 mg/kg/day) corresponded to about 5 times clinical exposure (based on AUC). The original submission indicated that possible mechanisms for these respiratory system tumours were to be investigated but studies have not been provided in the current Australian submission.

These two carcinogenicity issues were raised with the sponsor (on 6 January 2011). The sponsor's reply indicated that no additional carcinogenicity studies have been undertaken or

[2] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

were planned. The sponsor's response also included three developmental reports[3] investigating the possibility of a rodent-specific metabolite with mutagenic potential. These studies showed the existence of a new metabolite, Y-metabolite, which is a cytochrome P-450 (CYP)-mediated product of one of the major primary metabolites of rasagiline, trans-3-OH-PAI. The Y-metabolite is found in mouse plasma and urine, with lower levels in rat urine, but it had not been detected in human plasma or urine. The structure of Y-metabolite was established and confirmed, but attempts to synthesise sufficient quantities for genotoxicity testing were unsuccessful due to stability limitations. Thus, a possible link between Y-metabolite and rodent carcinogenicity findings remains unproven.

Reproductive toxicity

In the embryofetal development study, treatment of NZW rabbits was conducted over gestational days (GD) 7-19 (stages C and D of the reproductive process in a non-rodent species). Maternal toxicity at ≥ 6 mg/kg/day was characterised by reduced body weight (BW) gain/BW loss and food consumption, and at 36 mg/kg/day, by increased incidences of scant faeces and other adverse clinical findings (ungroomed coat, no faeces in the cage pan and soft or liquid faeces). This resulted in a No-Observed-Adverse-Effect-Level (NOAEL) of 1 mg/kg/day for maternal toxicity. Apart from abortion of two litters, there was no significant embryofetal toxicity at 36 mg/kg/day (the maximum dose tested). The findings (including toxicokinetics) were consistent with those in the embryofetal development studies conducted using Chinchilla rabbits provided with the previous, original Australian submission. In the original Chinchilla study with doses of 1, 7 and 45 mg/kg/day PO, there was maternal (reduced BW gain and food intake) and embryofetal (increased post-implantation loss, reduced fetal BW) toxicity at 45 mg/kg/day, with a NOAEL set at 7 mg/kg/day. In the NZW rabbit study submitted with the current Australian submission, clinical signs of toxicity (36 mg/kg/day) in addition to BW and food consumption effects (6, 36 mg/kg/day) were observed. Thus, the NZW does appear to be more sensitive to rasagiline treatment than the Chinchilla does, but this did not translate to greater incidences of fetal findings.

The findings in the currently submitted embryofetal toxicity study did not alter the toxicity profile of rasagiline mesilate.

Nonclinical Summary

Lundbeck Australia Pty Ltd has resubmitted an application to register rasagiline mesilate as a l mg tablet formulation for use in the treatment of Parkinson's Disease, either as monotherapy in patients with early disease or as adjunctive therapy in patients receiving concomitant levodopa/decarboxylase inhibitor therapy. There is no change to the proposed dose (1 mg/day), clinical use or formulation, relative to the original Australian submission. The current submission of nonclinical data consisted of a safety pharmacology study, a reproductive toxicity study, three analytical development studies, and published literature references. The results from these did not alter the nonclinical toxicity profile of rasagiline mesilate, as assessed with the previous application.

Conclusions and Recommendations

Nonclinical evidence for efficacy, including the evidence for inhibition of MAO-B by rasagiline mesilate as well as toxicological findings impacting on safety, was assessed with the original application. The newly submitted data included further evidence to show that the primary metabolite of rasagiline, aminoindan, also had neuroprotective activity. The nonclinical data submitted with the current application have no impact on the conclusions or recommendations made in the original nonclinical evaluation report.

[3] Post-Authorisation Commitment of 16 November 2004 requested by the CHMP: Y-metabolite mutagenicity studies *in vitro* and *in vivo*.

In the original submission, the sponsor flagged further investigations into the possible mechanisms for the respiratory system tumours in mice. A new metabolite (Y-metabolite) has been detected in mice and rats (but not humans) but its preparation for genotoxicity testing was not technically feasible and its genotoxic potential is unknown.

IV. Clinical Findings

Introduction

The studies submitted were performed according to the appropriate guidelines for Good Clinical Practice, and the Declaration of Helsinki. Clinical references cited in this AusPAR are listed at the end of the document (page 35).

Pharmacokinetics

There were two new clinical pharmacokinetics studies submitted with the current Australian application:

- **Study TVP-1012/432** Rasagiline pharmacokinetic study to investigate dose proportionality following multiple-dose administration and co-administration with levodopa/carbidopa in young and elderly healthy subjects, and
- **Study TVP-1012/433** Rasagiline mesylate pharmacokinetics after multiple oral dose administration in healthy subjects and subjects with moderate renal impairment.

The first study was performed to examine dose-proportionality for doses of 1, 2 and 6 mg, and to assess the effect of age and gender on both dose-proportionality and the bioavailability of rasagiline. In addition, previous studies had suggested either no or a small decrease in rasagiline clearance due to treatment with levodopa/carbidopa. This study was designed to further investigate the effect of levodopa on rasagiline clearance. The second study was designed to investigate the effect of moderate renal impairment on the pharmacokinetics of both rasagiline and its major metabolite aminoindan as there had been contradictory findings from previous studies in patients with either mild or moderate renal impairment.

Study TVP-1012/432

The primary objectives were to investigate the dose-proportionality of daily doses of rasagiline (1, 2 and 6 mg) following multiple-dose administration in young and elderly healthy subjects and to assess the effect of levodopa/carbidopa (single dose) on the pharmacokinetics of rasagiline. Secondary objectives were to evaluate orthostatic blood pressure and pulse rate timed to rasagiline dosing and monitor the safety of rasagiline following multiple oral dosing. The effects of age and gender were explored in parallel groups and a within group design was used for the drug-interaction study (Table 2). The 'young' group was aged from 40 to 60 years and the older group over 65 years. Both age groups received doses of 1, 2 or 6 mg rasagiline for 8 days except for the 'young' 1 mg group who received in addition both rasagiline and levodopa/carbidopa on Day 9. Plasma concentrations of rasagiline and aminoindan were measured using the same fully validated assay that was used in previous studies. Pharmacokinetic parameters calculated and statistical analyses were as described in Table 2.

The groups were closely matched for age, gender and body-mass index (BMI). Systolic and diastolic blood pressure (BP) values pre-study were generally within physiological limits applicable for the study populations under investigation, with BP values increasing with age. The pharmacokinetic profiles of rasagiline and aminoindan were similar to previous studies. Rasagiline was rapidly (10-20 mins) detected in the blood with peak levels reached by 20-30 minutes post dose. Rasagiline concentrations declined rapidly with a biphasic elimination pattern most obvious in the 6 mg groups. Trough levels of rasagiline were in general only detected after multiple doses of 6 mg. Aminoindan concentrations peaked at 1-1.75 hours and exceeded the plasma concentration of rasagiline after approximately 2 hours, with an apparent

slower elimination. Geometric mean pharmacokinetic parameters for rasagiline are listed by group and dose in Table 2.

Table 2. Pharmacokinetic study TVP-1012/432

Protocol no, dates, sites	Study Design	Dosage, duration of study	Subjects, inclusion criteria & demographics (mean, range)	Criteria for evaluation	Pharmacokinetic parameters and Results
TVP-1012/432 Feb 2006-May 2006 One German site	Phase 1 open-label, oral multiple dose study to investigate dose-proportionality in young (40-60 y) and old (>65 y) healthy volunteers. Effects of a single oral dose of LD/CD on rasagiline PK also investigated in the 1 mg young group. Subjects allocated sequentially to ascending dose groups and randomly within dose groups. Tyramine restriction diet followed during study.	6 groups all gender balanced: 1. Young 1 mg RAS for 8 d followed by 200/50 mg LD/CD on Day 9 2. Old 1 mg 3. Young 2 mg 4. Old 2 mg 5. Young 6 mg 6. Old 6 mg. Groups 2-6, all 8 days treatment. Group 6 hospitalised during study.	Good health, BMI 19-29 kg/m^2, BP <90 and <95 mmHg diastolic, <150 and <160 mmHg systolic for young and old groups respectively, negative alcohol, drug, cotinuine screens Enrolled n= 55, Completed n= 55 but 1 subject withdrawn due to positive cotinine test (14 group 1, 8 per other groups), 27M, 27F, young 53y (40-60), old 69y (65-77). All Caucasian	Plasma concentrations of RAS & AI measured by GC-MS. Pharmacokinetic variables $C_{max, ss}$, $t_{max, ss}$, $AUC_{\tau, ss}$, $t_{1/2}$, CL_{ss}/F, V_{ss}/F. Dose proportionality of $AUC_{\tau, ss}$ & $C_{max, ss}$ was evaluated for total population and for each gender and age group. Regression analysis used to calculate slope and 95% CIs. Inclusion of the value 1 within 95% CI limits indicated proportionality. Effect of LD/CD on RAS & AI $AUC_{\tau, ss}$, CL_{ss}/F & $C_{max, ss}$ evaluated for total group and each gender by 1-sample t-test on log-transformed values. Standard bioequivalence criteria used to assess 90% CIs of ratios of geometric means. Safety: AEs, clinical laboratory tests, vital signs including orthostatic blood pressure & pulse, ECGs, physical exams.	**Pharmacokinetic parameters for RAS:** $AUC_{\tau,ss}$: 5.5, 3.7, 17.7, 16.4, 61.8 & 67.4 ng.h/mL respectively for groups 1-6; C_{max} : 6.0, 4.8, 13.9, 11.6, 36.7 & 38.8 ng/mL; t_{max}: 0.5, 0.33, 0.33, 0.33, 0.5 & 0.5 h; $t_{1/2}$: 1.4, 1.0, 3.0, 4.1, 5.7 & 7.2 h; CL_{ss}/F: 182.3, 268.8, 113.3, 121.8, 97.1 & 89.1 L/h: V_{ss}/F: 539.3, 776.8, 421.2, 583.9, 447.1 & 580.7 L. **Dose proportionality:** $AUC_{\tau, ss}$: regression slope 1.4594; 95% CI 1.3156 – 1.6033. C_{max} : regression slope 1.0732; 95% CI 0.9314 – 1.2151 **Effect of LD/CD:** $AUC_{\tau,ss}$: ratio 1.075; 90% CI 0.989 – 1.169 CL_{ss}/F: ratio 0.930; 90% CI 0.856 – 1.011 C_{max} : ratio 0.973; 90% CI 0.841 – 1.127 **Safety assessments:** No deaths or SAEs. Only one AE was reported across all old groups (headache); 1, 9 & 8 AEs were reported for young groups (dizziness, headache). For group 1 after LD/CD on day 9, a further 23 AEs were reported (nausea, vomiting). No severe AEs, 28 (67%) thought possibly, 4 (9.5%) probably drug related. No clinically significant effect of RAS on haematology, clinical chemistry or urinalysis parameters, vital signs, ECGs or body temperature over time or by increasing dose level.

Dose proportionality was evident in the C_{max} measurements considering all subjects independent of age, gender or adjustment of dose to body weight. The increase in area under the plasma concentration time curve over a dosing interval at steady state ($AUC_{t, ss}$) was larger than expected both with and without adjustment of dose to body weight (Table 2). This was generally independent of age and gender (except for young males where a dose proportional increase was apparent). The extent of non-proportionality was greater between the 1 and 2 mg doses than the 2 and 6 mg doses.

There were no significant effects of a single-dose of levodopa/carbidopa on the pharmacokinetic parameters $AUC_{t,ss}$, C_{max}, and steady state oral clearance (CL_{ss}/F) of rasagiline for the group considered as a whole (Table 2). There were no significant effects of levodopa/carbidopa on the parameters $AUC_{t, ss}$ and C_{max} for the metabolite aminoindan. Broken down by gender, standard bioequivalence criteria were not met for some parameters but given the variation in pharmacokinetic parameters and the small numbers this may not be a meaningful analysis.

Multiple doses of 1, 2 and 6 mg of rasagiline over 8 days were safe and well-tolerated in both the young and elderly subjects. All adverse events (AEs) were mild or moderate in intensity with the most common being dizziness and headache. The co-administration of levodopa/carbidopa resulted in an increase in AEs, particularly gastrointestinal effects. No systematic trend in orthostatic blood pressure and pulse rate related to rasagiline dosing was apparent. None of the safety assessments including clinical chemistry, haematology, urinalysis, body temperature, vital signs or electrocardiograms (ECGs) showed any apparent effect of rasagiline either over time or with increasing dose.

Study TVP-1012/433

This study was an open, parallel group oral multiple dose study (Table 3). The primary objective was to compare the plasma pharmacokinetic parameters of rasagiline and aminoindan following once daily repeated dosing with a 1 mg tablet of rasagiline for 8 days in healthy subjects and subjects with moderate renal impairment (defined as a CL_{cr} of 30 - <50 ml/min). The secondary objective was to investigate the safety and tolerability of rasagiline in subjects with moderate renal impairment following once daily oral dosing for 8 days. Rasagiline was administered daily for 8 days to both groups. Pharmacokinetic parameters calculated and statistical analyses were as described in Table 3.

The two groups were well matched for age, gender and BMI (Table 3). The most commonly co-administered drugs in the renal impairment group were allopurinol, hydrochlorothiazide, and metoprolol succinate. In both groups, rasagiline concentrations appeared rapidly in the blood and peaked at 20 mins post-dose. Peak concentrations were lower (~18%) and elimination was slower in the renal impairment group. Peak aminoindan concentrations were similar in both groups but its elimination was slower in the renal impairment group. Mean pharmacokinetic parameters for both rasagiline and aminoindan are presented in Table 3. The primary variables for rasagiline, C_{max} and AUC_{τ}, both fell below the accepted bioequivalence criteria; C_{max} was lower in the renal impairment group whereas AUC_{τ} exposure was comparable in the two groups. Both primary parameters for aminoindan exceeded the bioequivalence criteria with both being higher in the renal impairment group (Table 3). Larger individual variations in the PK parameters were observed in the renal impairment group.

Doses of 1 mg rasagiline over 8 days were safe and well tolerated even in the renal impairment group where the type and incidence of AEs was similar to the healthy control group. The most common AEs were h eadache, drowsiness and nausea. None of the other safety assessments (including clinical chemistry, haematology, urinalysis, vital signs and ECGs) showed any apparent effect of rasagiline in either group.

Table 3. Pharmacokinetic study TVP-1012/433

Protocol no, dates, sites	Study Design	Dosage, duration & blood sampling schedule	Subjects, inclusion criteria, demographics (mean, range)	Criteria for evaluation	Pharmacokinetic parameters and Results
TVP-1012/433 Feb 2006-July 2006 1 site in Germany	Phase 1 open-label, parallel group, oral multiple dose study to investigate rasagiline and AI pharmaco-kinetics in healthy subjects and subjects with moderate renal impairment. Age (± 10y), weight (±10 kg) & gender matched Tyramine restriction diet followed during study.	Daily 1 mg rasagiline for 8 days in both groups. Blood sampling predose on days 1, 6 & 7. Blood sampling on day 8: pre-dose, 10, 20, 30, 40, 50, 60, 80, 100 & 120 min, 2.5, 3, 4, 6, 8, 12 & 18 h post-dose. Day 9: 24 h and 36 h post-dose. Day 10: 48h post-dose.	M or F, 25-70y. BMI 18-32 kg/m^2, non-smokers. Normal renal function defined as a CL_{cr} >80 ml/min and moderate renal impairment as CL_{cr} 30 to <50 ml/min. Latter group stable renal function >2 months. Enrolled/ Completed n=24, (12 per group), Healthy: 4F, 8M; 58y (40-68); renal: 4F, 8M; 60y (33-70).All Caucasian	Plasma concentrations of RAS & AI measured by GC-MS. Primary pharmacokinetic variables derived for both RAS & AI were AUC_{τ}, & C_{max}. Other parameters included t_{max}, AUC_{last}, & $t_{1/2}$. Protein binding measured for both RAS & AI ex vivo. AUC_{τ} & C_{max} compared by ANOVA between groups by calculation of geometric mean ratios (GMR) and 90% CIs. No difference between groups if the 90% CIs were within 80-125% for AUC_{τ} and 70-143% for C_{max}. Safety: AEs, clinical laboratory tests, vital signs, ECGs, physical exams.	**Parameters for RAS:** t_{max}: 0.40, 0.41 h respectively for healthy & renal impaired groups; C_{max} : 6.68, 5.49 ng/mL; $t_{1/2}$: 1.23, 1.37 h; AUC_{τ}: 5.52, 5.65 ng.h/mL; AUC_{last} : 4.96, 5.04 ng.h/mL; % protein bound: 81.1%, 78.8%. **Parameters for AI:** t_{max}: 1.56, 1.74 h respectively for healthy & renal impaired groups; C_{max} : 2.12, 2.42 ng/mL; $t_{1/2}$: 15.72, 19.00 h; AUC_{τ}: 25.38, 35.65 ng.h/mL; AUC_{last} : 26.05, 44.63 ng.h/mL; % protein bound: 33.6%, 29.7%. **ANOVA RAS:** C_{max} : GMR 79.0; 90% CI 59.1-105.7 AUC_{τ}: GMR 92.6; 90% CI 68.5 – 125.2. **ANOVA AI:** C_{max} : GMR 115.9; 90% CI 99.2-135.5 AUC_{τ}: GMR 140.9; 90% CI 115.3 – 172.2. **Safety assessments:** No deaths, 1 SAE of cholecystitis. 40 AEs reported, 18 (45%) from healthy & 22 (55%) from renal subjects. Most frequent headache, drowsiness, nausea. 1 severe AE (cholecystitis), 2 (5%) thought possibly, 24 (60%) probably drug related. No relevant differences in AEs between groups. One clinically significant leucocytosis possibly due to gastroenteritis, otherwise no clinically significant effect of RAS on haematology, clinical chemistry or urinalysis parameters, vital signs, ECGs or body temperature over time.

Evaluator's conclusions on pharmacokinetics

The studies were well-designed with adequate sample sizes and appropriate populations, inclusion/exclusion criteria including informed consent, restrictions on alcohol and xanthine containing beverages and concomitant medication. Analytical procedures involved well validated assays with good quality control. Statistical analyses were considered appropriate. Safety assessments were good with pre-specified reference ranges for the laboratory tests.

The pharmacokinetic profile of rasagiline (and aminoindan) was not obviously altered by the data from the new studies. The first study showed that there is no effect of age, gender or concomitant administration of levodopa/ carbidopa (LD/CD) on the pharmacokinetics of rasagiline or aminoindan. However, the plasma exposure (AUC) was not dose-proportional between the 1 and 6 mg doses. The second study found that renal impairment led to a decrease in rasagiline concentration (and an increase in aminoindan concentration). However, rasagiline plasma exposure, as measured by AUC, was still comparable between the groups. These results confirmed the results of a previous study of moderate renal impairment. The new studies suggest that dosage alterations are not required in the elderly, those taking LD/CD or those with moderate renal impairment.

Pharmacodynamics

Two new pharmacodynamic studies were submitted:

- **Study TVP-1012-120-TYR.** A Phase 1, double blind, placebo controlled, randomised (within each group) study to evaluate the interaction between orally administered tyramine hydrochloride and rasagiline mesylate in healthy subjects, and
- **Study TQT-TVP-1012-121.** A double blind, randomised, parallel group, multiple dose, thorough QT/QT_c trial in healthy subjects to assess the effects of clinical and supratherapeutic doses of rasagiline on cardiac repolarisation.

The first study provided additional data on the potential interaction between rasagiline and tyramine. A comparison was made between the effect of escalating doses of tyramine on systolic blood pressure (SBP) at baseline and after achieving a steady state of plasma rasagiline concentrations with doses ranging from 1 mg to 6 mg per day. The second study investigated the effect of therapeutic and supratherapeutic doses of rasagiline on QTc prolongation.[4]

Study TVP-1012-120-TYR

The primary objective of this study was to assess tyramine sensitivity when administered with rasagiline and the selectivity of rasagiline for MAO-B. The secondary objective was to investigate orthostatic BP and pulse, timed to rasagiline dosing. The study was double blind, placebo controlled and randomised within each group (Table 4). It involved three periods of study:

1. The first 10 days involved escalating the tyramine dose until an increase in SBP of ≥30 mmHg from baseline was reached;
2. Treatment with either phenelzine (positive control), selegiline (comparator), rasagiline or placebo;
3. A repeat of the tyramine testing (detailed in 1) whilst maintaining the treatment (as detailed in 2) (Table 4).

[4] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Subjects who did not achieve the required increase in SBP at the maximum tyramine dose during Period 1 were excluded from the rest of the study. Rasagiline doses of 1, 2, 4 and 6 mg/day were administered. All but one group (the 2 mg/day group) were treated for 14 days in Period 2. The 2 mg/day group was studied over both 14 and 30 days. Blood samples were collected for measurements of plasma dihydroxyphenolglycol (DHPG; to assess MAO-A activity) and tyramine, rasagiline and aminoindan levels at appropriate times and using fully validated methods.

The groups were well matched for age, gender and BMI (Table 4). No differences in tyramine interaction were noted in the two groups treated for 14 and 30 days with 2 mg rasagiline (unblinded analysis). It was therefore considered that steady-state conditions had been achieved by Day 14. All other groups were treated for this time period of 14 days. Some subjects took concomitant medication during the study, consisting mainly of labetolol to treat tyramine related hypertension and paracetamol.

The mean TYR30[5] ratio was highest in the positive control (phenelzine) group and lowest in the placebo (PBO) group (Table 4). All drugs were statistically different to the pooled PBO group. Similar TYR30 ratios were observed for selegiline and the 1 and 2 mg doses of rasagiline. The selectivity for MAO-B appears to be lost at the higher doses of rasagiline and this was confirmed by the plasma DHPG measurements. Phenelzine, selegiline and the 4 mg and 6 mg doses rasagiline inhibited MAO-A (as shown by decreased mean plasma DHPG concentrations). In contrast, the effect of the lowest rasagiline dose (1 mg) was similar to that of PBO (small increase) whilst the 2 mg dose showed no effect (at 14 days) or a small decrease (at 30 days) in MAO-A activity. There was no evidence of an increased rate of orthostatic hypotension in rasagiline treated subjects compared to PBO treated subjects or of a dose response effect for rasagiline (Table 4).

Tyramine plasma concentrations increased with increasing doses reaching a peak around 0.25 to 0.5h with a wide inter-individual variation in C_{max}. Due to the few sampling points pharmacokinetic analysis was not considered useful. Rasagiline and aminoindan pharmacokinetics were similar to previous studies and similar profiles were obtained for the 2mg groups again confirming steady state conditions were reached by day 14. Longer half-lives were estimated for 4 and 6 mg rasagiline than for the lower doses largely due to plasma concentrations below the assay detection limit from 8h post-dose for the 1 and 2 mg doses.

Rasagiline at 1- 6 mg/day was well tolerated. The majority of AEs were of mild intensity with only three SAEs during the study. During Period 1 there was one event of ventricular tachycardia and in Period 3 there was one instance of intervertebral discitis and one of acute coronary syndrome. The latter was considered as possibly related to the tyramine administration. None were considered to be related to rasagiline. During Periods 2 and 3 the most common AEs were headache, dizziness, nausea and fatigue. No apparent effects of rasagiline on any of the other safety assessments (including clinical chemistry, haematology, urinalysis, vital signs or ECGs) were noted.

[5] The tyramine dose associated with an increase from baseline in SBP of ≥ 30 mm Hg maintained for at least three consecutive readings over 10 minutes or more.

Table 4. Pharmacodynamic study TVP-1012-120-TYR

Potocol no, dates sites	Study Design	Dosage and duration of study	Subjects inclusion criteria & demographics (mean, range)	Criteria for evaluation	Results
TVP-1012-120-TYR Dec 2006 – Feb 2008 One site in The Nether-lands	Double blind, PBO controlled, randomised (within each group), positive & comparator controlled, multiple dose study in healthy subjects. Period 1: tyramine challenge test with escalating doses (25-800 mg) over 10d. Period 2: treatment with MAOI or PBO for 14 or 30 d. Period 3: treatment plus tyramine challenge (Grp1 5-105 mg, others 12.5-800 mg). Step 1: Groups 4a & 4b commenced first, Step 2: other groups followed. Tyramine restriction diet.	Group 1: 45 mg/d phenelzine Group 2: 10 mg/d selegiline & matching PBO, ratio 2:1 Group 3: 1 mg/d RAS & PBO Group 4a, 4b: 2 mg/d RAS & PBO Group 5: 4 mg/d RAS & PBO Grp 6: 6 mg/d RAS & PBO. All groups 14 days except 4b (30 days).	M or F ratio 60/40, 25-70y. BMI 19-30 kg/m^2, smokers 15% per group. Randomised: n=156, completed: n=149 Grp 1 : n=16, 9M 7F, 57y (40-68) Grp 2 : n=22, 11M 11F, 53y (40-68) Grp 3 : n=23, 9M 14F, 60y (45-69) Grp 4a : n=24, 14M 10F, 60y (44-70) Grp 4b : n=23, 11M 12F, 61y (47-69) Grp 5 : n=24, 14M 10F, 55y (41-70) Grp 6 : n=24, 14M 10F, 57y (40-70) 92% Caucasian	Primary outcome: TYR30 ratio, calculated as the tyramine dose causing an increase of SBP ≥30 mmHg for ≥3 readings over ≥10 mins in period 1, divided by the dose causing the same change in period 3. Comparisons using Wilcoxon rank test. Secondary outcome: orthostatic hypotension defined as change in BP from supine to standing of SBP ≥20 or ≥40 mmHg & DBP ≥10 or ≥20 mmHg following RAS dosing Pharmacodynamics: change in plasma DHPG concentrations from day 1 to Day 24/40. Pharmacokinetics (PK): plasma tyramine, RAS and AI concentrations & PK parameters (including C_{max}, AUC_{last}, $t_{1/2}$). Safety: AEs, clinical laboratory tests, ECGs, vital signs, physical exams.	**Primary outcome**: Geometric mean TYR30 ratios were phenelzine 17.32, selegiline 2.47, 1 mg RAS 2.03, 2 mg RAS (4a) 3.33, 2 mg RAS (4b) 2.45, 4 mg RAS 4.50, 6 mg RAS 5.10, pooled PBO 1.50. All drug groups significantly greater than pooled PBO ($p< 0.05$). **Secondary outcome**: Maximum rates of orthostatic hypotension (DBP ≥ 10 mmHg) on the last day of period 2 at any time post-dose: 53% (PBO), 31% (1 mg), 43% (2 mg), 77% (4 mg) & 33% (6 mg) cf pre-dose: 16%, 13%, 14%, 12% & 27% respectively. Incidences of DBP ≥ 20 mmHg or SBP ≥ 20 or 40 mmHg were ≤ 3 subjects per group. **Pharmacodynamics**: Decreases in DHPG in order of magnitude were phenelzine > 4 mg RAS > 6 mg RAS > 2mg RAS (4b) > selegiline >2 mg RAS (4a) > 1 mg RAS = PBO. **PK measures**: Tyramine plasma concentration showed wide variability. PK profile of both RAS & AI similar to previous studies. Both C_{max} and AUC values for RAS & AI increased with dose. Similar PK profiles for both 2 mg groups. Elimination phase for 1, 2 mg not estimable due to low concentrations, mean $t_{1/2}$ for 4, 6 mg doses 4.74, 6.78h. **Safety measures**: No deaths. 3 SAEs: VT (tyramine), discitis (2 mg RAS & tyramine), acute coronary syndrome (6 mg RAS & tyramine). 5 DAEs: VT, ST segment depression, ectopic ventricular beats, AV block (all tyramine), influenza (6 mg RAS & tyramine). 564 AEs reported for periods 2 (51%) & 3 (49%): most frequent headache, dizziness, nausea, fatigue. 2 severe AEs (discitis, disturbance in attention). No clinically significant effect of RAS on haematology, clinical chemistry or urinalysis parameters, vital signs or ECGs.

Study TQT-TVP-1012-121

The study was randomised, double blind and PBO controlled (Table 5). It involved a thorough investigation of cardiac repolarisation by measurement of the QTc interval before and after 10 days treatment with 1, 2 and 6 mg rasagiline. Moxifloxacin was used as a positive control. The primary objective of the study was to investigate any effects of clinical (1 mg/day) and supratherapeutic (2 and 6 mg/day) doses of rasagiline on QTc prolongation. The secondary objective was to compare the effects moxifloxacin (400 mg) on QTc prolongation in order to demonstrate the sensitivity of the methods. Plasma concentrations of rasagiline and aminoindan were determined in order to investigate the relationship between the pharmacodynamic and pharmacokinetic parameters (Table 5).

The groups were well matched for age, gender and BMI (Table 5). The time-matched analysis for the QTc primary endpoint revealed that all doses of rasagiline met the non-inferiority test between PBO and rasagiline (the upper confidence intervals (CIs) that were below the defined cut-off of 10 ms prolongation). The results from the moxifloxacin group confirmed the assay sensitivity. There was no clear pattern of effect of rasagiline on HR, atrioventricular (AV) conduction or cardiac depolarisation as measured by PR or QRS intervals. There were a few minor ST-T changes across all groups. The slopes of the plots of plasma rasagiline and aminoindan versus QTc did not indicate any significant relationship between these variables. Overall, the results support the conclusion that there is no effect of rasagiline on HR, PR, QRS interval or QTc interval. The rasagiline and aminoindan pharmacokinetic results were similar to those of previous studies; C_{max} increased proportionally with the dose and the AUC showed a greater than dose proportional increase. Again, the terminal elimination half-life for rasagiline increased with increasing dose.

It was concluded that 1- 6 mg/day of rasagiline was well tolerated. The majority of AEs were of mild intensity. The most common AEs were headache and dizziness. There were no SAEs reported during the study. None of the other safety assessments (including clinical chemistry, haematology, urinalysis, vital signs or ECGs) showed any apparent effect of rasagiline.

Evaluator's conclusions on pharmacodynamics

The studies were well-designed with appropriate populations studied, adequate sample sizes and appropriate inclusion/exclusion criteria including informed consent, restrictions on alcohol, smoking and xanthine-containing beverages and concomitant medication. Analytical procedures involved well validated assays with good quality control. Pharmacokinetic measurements used an appropriate non-compartmental model and statistical analyses were considered to be appropriate. The 10 msec QTc cut off is considered to be the accepted threshold for declaring the study negative for effects on cardiac repolarisation. Safety assessments were performed before treatment, during the study and at follow up assessments.

Study **TVP-1012-TYR-120** confirmed that at the lower (1 and 2 mg) doses rasagiline shows selectivity for MAO-B. This selectivity was lost at the higher doses. This suggests that a low-tyramine diet is not required for these dosage levels. Study **TQT-TVP1012-121** showed that rasagiline had no effects on cardiac repolarisation.

Table 5. Pharmacodynamic study TVP-1012-121

Protocol no, dates sites	Study Design	Dosage and duration of study	Subjects inclusion criteria, demographics (mean, range)	Criteria for evaluation	Results
TVP-1012-121 June 2008 – Oct 2008 1 site, USA	Double blind, double-dummy, PBO controlled, randomised, parallel multiple dose study in healthy subjects. ECGs obtained on day -1 and day 10 for measurement of QTc prolongation. Study consisted of a screening visit, in-house study period and follow up visit. 12-lead ECGs at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 223.5 on days 1 & 10. Tyramine restriction diet.	Group 1: 1 mg/d RAS Group 2: 2 mg/d RAS Group 3: 6 mg/d RAS Group4: PBO Group 5: PBO & 400 mg moxiflox-acin single dose on day 10 All groups 10 days.	M or F ratio 50/50, 18-45y. BMI 19-30 kg/m^2, non-smokers. Resting QTc between 300 & 450 (M) or 470 (F) msec. Randomised: n=250, completed: n=247 Grp 1 : n=51, 24M 27F, 24y (18-45) Grp 2 : n=49, 23M 26F, 22y (18-39) Grp 3 : n=49, 23M 26F, 24y (18-45) Grp 4 : n=50, 23M 27F, 24y (18-45) Grp 5 : n=51, 24M 27F, 22y (18-45) 86% Caucasian	Pharmacodynamics: Primary endpoint defined as the time-matched change from baseline in individual QTc (QTcI). QTcI obtained from individual slopes of QT/RR from baseline ECGs. Non-inferiority test between RAS & PBO such that the null hypothesis rejected if QTcI (PBO corrected change from baseline) at any time points have two-sided upper limit of 90% CIs > 10 msec. Assay sensitivity established if lower limit of two-sided 90% CIs > 5 msec for moxifloxacin cf PBO. Secondary endpoints: QTcF, QTcB, outlier analysis of HR, QT & PR, QRS, QTcI, QTcF, QTcB intervals & morphology analyses. Pharmacodynamics/ pharmacokinetics: The relationship between time-matched change from baseline in QTc intervals & plasma concentrations calculated using mixed-effect model. Model used to predict QTc at C_{max} for each dose. Pharmacokinetics: Plasma concentrations of RAS & AI measured by GC-MS. Standard pharmacokinetic parameters calculated. Safety measures: AEs, clinical laboratory tests, ECGs, vital signs, physical exams.	**Primary endpoint:** Time matched analysis showed for all RAS doses upper 90% CIs that were below 10 msec. Assay sensitivity was established with moxifloxacin as 11/13 points exceeded 5 msec. Outliers were ≤ 2 subjects per group & new morphology changes were ST depression & T wave abnormalities in ≤ 2 per group. The slope for the QTcI v plasma concentrations was flat to negative for both RAS & AI. Predicted QTc at Cmax were 2.7, 2.1, 0.10 msec respectively. **Pharmacokinetic parameters RAS:** t_{max} 0.5 h all doses; C_{max} 5.4, 13.0, 40.9 ng/ml; AUC_{last} 7.3, 23.4, 77.9 ng.h/ml; $t_{1/2}$ 1.8, 5.0, 6.9 h respectively. **Pharmacokinetic parameters AI:** t_{max} 2.0 h all doses; C_{max} 2.2, 5.0, 15.1 ng/ml; AUC_{last} 30.6, 72.9, 215.3 ng.h/ml; $t_{1/2}$ 12.0, 11.3, 10.7 h respectively. **Safety measures:** No deaths, no SAEs, 2 DAEs depression, low back/side pain both RAS 2mg. 13 (26%) subjects 1 mg RAS, 16 (33%) 2 mg RAS, 14 (29%) 6 mg RAS, 18 (36%) PBO, 4 (8%) moxifloxacin. Headache & dizziness most common in all groups. One pregnancy 6 mg RAS, outcome unknown. No clinically significant effect of RAS on haematology, clinical chemistry or urinalysis parameters, vital signs or ECGs.

Efficacy

No new studies submitted. Clinical efficacy based on studies submitted with the previous submission for this product.

Safety

Introduction

The submission included one new study, Study TVP-1012-500, which was a multi centre, double blinded, randomised start, placebo controlled, parallel group study to assess the ability of rasagiline therapy to slow the clinical progression of the disease in early Parkinson's disease subjects.

The sponsor submitted a revised Integrated Summary of Safety (ISS) dated January 2009 and a Summary of Clinical Safety dated March 2010 which was based on the ISS. An overview of safety (Overview of Safety: Safety Statements on Melanoma) containing a description of the planned retrospective study of melanoma rates in rasagiline and non-rasagiline treated PD patients as well as a melanoma safety update dated September 2009 which contained similar data to the ISS were also included with the current Australian submission.

Study TVP-1012-500

The study consisted of a 36 week PBO controlled phase and a 36 week active treatment phase with both 1 mg and 2 mg doses of rasagiline (Table 6). Patients with a recent diagnosis of PD were included and those subjects who were diagnosed with melanoma, a history of melanoma or refusal to undergo biopsy of suspicious lesions at screening were excluded. The criteria for tolerability and safety evaluations are detailed in Table 6.

The revised ISS updated the adverse reactions profile for two cohorts:

1. the pooled monotherapy cohort consisting of the data from three previously submitted PBO controlled trials and the PBO controlled phase of study **TVP-1012-500,** and
2. the cohort of PD patients exposed to rasagiline in previous clinical trials with data from **TVP-1012-500** and from completed open-label extension trials.

Patient Exposure

Safety data were reported as a comparison of the pooled PBO groups and the 1 mg and 2 mg rasagiline groups for Phase 1 of Study **TVP-1012-500** (Table 6). A further analysis was presented for all rasagiline-exposed subjects (RAS cohort) from both phases of the study. During Phase 1, a total of 487 patients completed 36 weeks on rasagiline treatment. This resulted in 187.2 (1 mg) and 187.2 (2 mg) patient years of exposure. Altogether for the RAS cohort, 1070.5 patient-years were accumulated: 529.0 for 1 mg and 541.4 for 2 mg, with 472 subjects completing 36 weeks and a further 482 completing 72 weeks on either 1 or 2 mg rasagiline.

Table 6. Safety Study TVP-1012-500 (ADAGIO)

Protocol no, dates, sites	Study Design	No of subjects & demographics (Mean, range)	Diagnosis & inclusion criteria	Criteria for evaluation	Results
TVP-1012-500 Nov 2005 - April 2008 129 sites across 14 countries	A multi centre, double blind, randomised start, placebo controlled, parallel-group study. The study consisted of 2 phases: phase 1- a 36 week PBO controlled phase; phase 2 - a 36-week active-treatment phase. Subjects randomised to either of 4 groups: Group 1: PBO phase 1, 1 mg/d phase 2, delayed start, Group 2: 1 mg/d RAS during both phases, early start, Group 3: PBO phase 1, 2 mg/d phase 2, delayed start, Group 4: 2 mg/d during both phases, early start. During phase 1 if subject required additional anti-PD subject to proceed to phase 2. Assessments at weeks 12, 24, 36, 42, 48, 54, 60, 66 & 72. No additional anti-PD during phase 2.	n= 1338 screened n= 1176 randomised n= 1174 ITT Group 1: n= 298, 185M 113F, 62y (34-81) Group 2: n= 288, 175M 113F, 62y (32-81) Group 3: n= 295, 182M 113F, 62y (35-81) Group 4: n= 293, 175M 118F, 62y (31-79) 98% Caucasian n=1091 entered Phase 2, n=954 completed Phase 2.	M or F, 30-80y, diagnosis of PD confirmed by ≥ 2 of resting tremor, brady-kinesis, rigidity. If no tremor, unilateral onset & persistent asymmetry required. Early PD <1.5y from diagnosis & not requiring PD Rx at enrolment or for the next 9 months.	**Tolerability:** No (%) of discontinuations & no (%) of DAEs. **Safety:** AEs at all visits; biochemistry, haematology & urinalysis at screening, baseline, weeks 12, 36, 54 & 72; vital signs at all visits; home BP monitoring pre- meal & twice post-meal for 7 days prior to baseline & weeks 4 & 36; ECG at screening, baseline week 36 & week 72; physical & neurological exam-ination at screening & weeks 36 & 72; skin examinations at screening & weeks 36 & 72. Data reported for phase 1 for pooled PBO vs 1 mg & 2 mg RAS. Also all subjects from both phases exposed to RAS (RAS cohort).	**Discontinuations:** Group 1 22.5%, Group 2 17.4%, Group 3 18.3%, Group 4 16.7%. Most common for all groups was need for additional anti-PD Rx. **Incidence of AEs:** Phase 1: 68% PBO, 65.3% 1 mg, 68.3% 2 mg. Most common: fatigue 1 mg, back pain both RAS groups, headache all groups. One death: cerebral haemorrhage (1 mg). SAEs: 3.7%, 4.2%, 4.4% respectively; >1 subject fall (1 mg). DAEs: 2.9%, 3.1%, 3.4%; >1 subject fatigue, abdominal pain, nausea (PBO), fatigue (1 mg), headache (2 mg). RAS cohort: AEs: 72.4% 1 mg, 76.6% 2 mg. Most common: back pain, headache, fall 1 mg; fall, arthralgia, nasopharyngitis 2 mg. One death: aortic aneurism (1 mg early start). SAEs: 6.6% 1 mg, 7.7% 2 mg; >1 subject chest pain, angina pectoris, fall, pyrexia, pneumonia (1 mg), MI, dehydration, osteoarthritis, knee arthroplasty (2 mg). DAEs: 3.0% both; >1 subject fatigue (1 mg), headache, depression, dizziness (2 mg). **Clinical laboratory results**: mean levels similar across groups & time. Shift to PCSA values: ≤3% for any parameter for either RAS group. No clinically important differences for biochemistry, haematology or urinalysis. No clinically relevant differences across groups and time for BP, pulse & orthostatism. Mean weight similar across groups & time. ECGs: mean HR, PR, QRS, QTc intervals similar across groups & time. QTcB ≥ 30 msec similar across groups: no QTcB ≥60 msec, shifts from <450 -450-480 msec similar, 1 shift to ≥500 msec. One case of melanoma (RAS, 1 mg early start).

The ISS pooled PBO controlled monotherapy cohort was updated to 876 rasagiline-treated subjects representing 501.1 patient-years of exposure to rasagiline; 251.4 patient-years of exposure to 1 mg and 249.7 patient-years of exposure to 2 mg. The PD patients ever exposed to rasagiline in clinical trials cohort was updated to 2487 subjects for a total of 4347 patient years of exposure to rasagiline. Of these, over 50% (n=1279) were exposed for ≥ 12 months, with a further 495 subjects exposed for ≥ 2 years and 429 subjects treated for ≥ 3 years. The majority of subjects (>90%) were exposed to at least 1 mg rasagiline and of these 63% were male and their mean age at treatment initiation was 63 years (range 31-92).

Adverse Events

During Phase 1 of Study **TVP-1012-500** the proportion of subjects with at least one treatment emergent adverse event (TEAE) was similar across the study groups: 68% of the PBO group and 65.3% and 68.3% of the 1 mg and 2 mg groups, respectively. For the overall RAS cohort, the two rasagiline groups again reported similar incidences of AEs (72.4% and 76.6%). Commonly reported AEs during Phase 1 (>10 subjects and 1.5 times greater incidence than PBO) for the 1 mg group were fatigue and constipation. In the 2 mg group, muscle spasms, cough, fatigue and upper respiratory tract infection were reported. Of these, only fatigue and constipation might result from increased dopaminergic activity. The most common AEs for the RAS cohort are shown in Table 6.

The majority of AEs were mild (57% in Phase 1 and 66% in the RAS cohort) or moderate (30% in Phase 1 and 37% of the RAS cohort) and the reported rates were similar across treatment groups. The incidence of AEs was higher in females (72%) than males (64%) and higher in older (>65 years) than younger subjects (71% compared to 65%). AEs of clinical significance investigated included: supraventricular arrhythmias, cardiac conduction disorders, heart failure, coronary artery disorders, cerebrovascular AEs, chest pain, hypertension, fall and syncope.

There were no obvious differences between the PBO and the 1 mg and 2 mg rasagiline groups in the incidence of these AEs. A malignant melanoma was discovered in one subject on 1 mg rasagiline at Week 72.

In the ISS pooled monotherapy cohort, the proportion of subjects with at least one AE was 70.3% for the PBO group, 71.2% for the 1 mg rasagiline group and 81% for the PD patients ever exposed to rasagiline in the clinical trials cohort. The most commonly affected body system (System Organ Class (SOC)) was Nervous System Disorders (21.0%, 23.6%, 40.8%), Infections and Infestations (20.2%, 22.9%, 35.4%) and Musculoskeletal and Connective Tissue Disorders (19.8%, 19.0%, 34.8%) for the PBO, 1 mg and all rasagiline exposed cohort, respectively. Commonly reported AEs for the pooled monotherapy cohort were headache, asthenia, dizziness, musculoskeletal pain, constipation, insomnia, influenza, oedema, bloating, neck pain, vertigo, febrile disorders, allergic conditions, viral infections, nasal congestion and rash. Common AEs in PD patients ever exposed to rasagiline in clinical trials cohort were fall, back pain, dizziness, nausea, arthralgia, insomnia, constipation, nasopharyngitis, headache and peripheral oedema.

In the ISS pooled monotherapy cohort, the incidence of AEs was higher in females (75%) than males (69%), higher in older (>65 years) (75%) than in younger (≤65) (68%) subjects and higher in subjects from North America (80%) than in subjects from the other countries which participated in the study (57%).

Serious adverse events and death

Two deaths occurred during Study **TVP-1012-500**. One subject on 1 mg rasagiline died from a cerebral haemorrhage during Phase 1. A second death occurred during repair surgery for an aortic aneurysm during Phase 2 whilst on 1 mg rasagiline. The first death was considered as unlikely to be related to study drug. The second was not considered to be related to study drug.

During Phase 1 of Study **TVP-1012-500,** the incidences of serious AEs (SAEs) were similar across the three groups: 3.7% (PBO), 4.2% (1 mg) and 4.4% (2 mg). For the RAS cohort, rates of SAEs were 6.6% and 7.7% for the 1 and 2 mg groups, respectively. In the latter cohort, only 2-3 patients per group experienced chest pain, angina pectoris, pyrexia, fall, pneumonia (1 mg) and myocardial infarction, dehydration, osteoarthritis and knee arthroplasty (2 mg). Of these, only chest pain in one subject and myocardial infarction were considered to be possibly related to study drug.

The overall death rate for the pooled monotherapy cohort from the ISS was 2.0 and 0.0 per 1000 patient-years for rasagiline and PBO subjects, respectively. Considering all PD patients ever exposed in the clinical trials cohort, the death rate was 8.5 cases per 1000 patient-years of rasagiline use. The rate of SAEs for the pooled monotherapy cohort was 3.5% in the PBO group and 4.1% in the 1 mg group and included angina pectoris, chest pain, fall and atrial arrhythmia. For all PD patients ever exposed to rasagiline in the clinical trials cohort, the most common SAEs were fall, PD, pneumonia and hip fracture.

Laboratory findings

Mean changes (from baseline to last observed value) in all biochemical parameters were similar across all treatment groups in Study **TVP-1012-500**. Percentages of patients with a shift to abnormal values at any time during Phase 1 were in general similar across all groups. Higher incidences of low calcium (0.69%, 1.41%, 1.39%), low sodium (0.86%, 0.70%, 2.78%) and high gamma glutamyl transferase (GGT) (2.76%, 3.87%, 6.94%), high aspartate aminotransferase (AST) (2.24%, 2.83%, 4.51%) and high alanine aminotransferase (ALT) (2.24%, 2.12%, 5.90%) were however noted in the PBO, 1 mg and 2 mg groups, respectively. These shifts were generally greater in the 2 mg rasagiline group than in the other two groups. A shift to individual, potentially clinically significant abnormalities (PSCAs) at any time during the study was less than ≤3% for any parameter and was not considered clinically meaningful.

Mean changes (from baseline to last observed value) in all haematological parameters during the study were similar for all treatment groups. Percentages of patients with a shift to abnormal values at any time during Phase 1 were in general similar across all groups. The rasagiline groups showed higher incidences of low haemoglobin (7.89%, 9.12%, 15.57%) and low haematocrit (9.09%, 11.58%, 13.49% in the PBO, 1 mg and 2 mg rasagiline groups, respectively) compared to the PBO group. Shifts to individual PSCAs at any time during the study was less than <2% for any parameter and was not considered clinically meaningful.

Mean changes (from baseline to last observed value) in vital signs were also similar across all treatment groups during the study. The incidence of orthostatic hypotension or vital sign outliers was similar across the groups with no clinically relevant differences. Home BP measurement showed that a mean decrease in BP and pulse occurred following a mean (pre to post prandial) at all time points in all groups. The incidence of outliers and maximal pre to post prandial increments/decrements in BP or pulse were not different between the groups.

Mean changes in HR and ECG intervals were similar across all the treatment groups during the study. The incidence of ≥ 30 ms (from baseline) change in QTcB/QTcF was 5.1%, 6.7%, 6.2% and 2.9%, 5.3%, 5.5% in the PBO, 1 mg, 2 mg rasagiline groups, respectively. There were no shifts ≥ 60 ms and the measured shifts (to 450-480 ms) were similar across the groups. Only one subject had a shift >50 ms.

There was only one patient diagnosed with melanoma during the study. This patient had been treated with rasagiline. This represents a rate of 0.9 subjects per 1000 patient years which can be compared to rates of 6.7 and 4.5 subjects per 1000 patient years of rasagiline and PBO exposure, respectively, in the original clinical development program. Non-melanoma skin cancers were diagnosed in 7 PBO and 20 rasagiline subjects. This represents rates of 19.4 and 18.7 per 1000 patient years, respectively. There were no clinically significant differences in clinical chemistry or ECG parameters or vital signs reported from the RAS cohort as compared

to those from Phase 1. Furthermore, there does not appear to be any clinically meaningful rasagiline dose related changes.

Safety in special populations

Safety data from the PK Study **TVP-1012/432 (**subjects >65 years) and Study **TVP-1012/433** (renally impaired subjects) were considered. The ISS contained an analysis of AEs for the pooled monotherapy cohort by gender, age (<65 years compared with ≥65 years) and by geographical location. The incidence of AEs was higher in females, in the older age group and in subjects from North America. However, none of the group differences were considered to be clinically meaningful.

Safety related to drug-drug interactions and other interactions

Safety data from the PK Study **TVP-1012/432** (of rasagiline/ levodopa/carbidopa) and Study **TVP-1012-120-TYR** (of tyramine challenge) have been discussed above. Whilst there were no reports of a serotonin syndrome from concomitant use of antidepressants and rasagiline, the ISS reports six cases of serotonin syndrome associated with concomitant use of rasagiline and antidepressants/selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs). Similarly there were no reports of a tyramine interaction in Study **TVP-1012-500** in which there was no tyramine restriction but three confirmed cases of tyramine interaction are evident from post-marketing experience.

Discontinuations due to adverse events

The incidence of AEs leading to treatment discontinuation (DAEs) in Phase 1 of Study **TVP-1012-500** were across the groups: 2.9% (PBO), 3.1% (1 mg), 3.4% (2 mg) and 3.0% (for both RAS cohorts overall). Two PBO subjects experienced fatigue, nausea, abdominal pain and two patients treated with rasagiline reported fatigue (1 mg) and headache (2 mg). For the RAS cohort, two subjects discontinued due to fatigue (1 mg) and headache, depression, dizziness (2 mg).

The incidence of DAEs for the ISS pooled monotherapy cohort were 2.7%, 3.7% 1 mg, and 9.4% for PBO, 1 mg rasagiline and the PD patients ever exposed to rasagiline in clinical trials cohort, respectively. The most common DAEs for both cohorts were dizziness and hallucinations.

Post marketing experience

The seventh Periodic Safety Update Report (PSUR) from January 2009 to January 2010 was submitted. Based on global marketing estimates, approximately 122,404 patients have been exposed to rasagiline each month during the last 6 months of the PSUR period. This resulted in an estimated 264,300 patient years of exposure. In addition, a further 1409 patient have participated in clinical trials or in compassionate use programs during this period.

A total of 233 medically confirmed events were reported in the seventh PSUR. These were obtained from spontaneous reporting, clinical trials, solicited programs, post-marketing studies or literature searches and considered by the investigators or the sponsor to be drug-related. These were broken down into:

- 97 serious events (64 of which were serious unlisted and 33 were serious listed) stemming from 52 cases,
- 89 non-serious unlisted events stemming from 51 cases with 47 non-serious listed events stemming from 26 cases.

Hence, altogether 233 events in 129 cases were evaluated. The Company Core Data Sheet (CCDS) edition number 2, 2007 was the reference used to determine whether events were listed or unlisted for this period. It has since been updated with further data on serotonin syndrome, tyramine related interactions and overdose symptoms (edition 3, 2009). The largest number came from the SOC Nervous System Disorders (n=53), followed by Psychiatric Disorders (n=37)

and General Disorders and Administration Site Conditions (n=32). Cumulative, serious, unlisted and confirmed reports which were assessed as treatment related and received from all sources were also analysed. The same three SOCs as previously listed were again the most common.

Events of interest from various SOCs were evaluated with rates from the current PSUR and compared to the previous PSUR. Similar incidence rates were found for cytopenia, loss of consciousness, dizziness, vertigo, peripheral oedema and pain in extremity whereas decreased rates for myocardial infarction, coronary artery disease, congestive heart failure, atrial fibrillation, nausea, syncope, arthralgia, convulsion/seizures, hypertension and hypotension were noted. Increased rates for fall (5.3 compared to 4.6 per 100,000 patient-years) were reported. Rates for melanoma increased from 0.65 to 1.1 per 100,000 patient years. However, this involved three cases in the entire post-marketing period and was less than the reference rates for both the US and United Kingdom (UK) populations. The majority of the above events have already been listed in the CCDS or their incidence rates were low compared with rates in PD populations or the general adult population and were thus not considered as requiring listing.

A total of nine medically confirmed reports of drug-interactions were received during the 2009-2010 PSUR period. Two serious reports concerned an interaction with linezolid (an antibiotic with MAO inhibiting properties) leading to increased BP and an interaction with warfarin leading to an increased international normalized ratio[6] (INR) and shakiness. Non-serious, possible interactions between rasagiline and pramipexole, duloxetine, mirtazepine, bupropion (n=2), ciprofloxacin and carbidopa/levodopa were also reported. There were three cases of serotonin syndrome reported during the 2009-2010 PSUR period with all cases assessed as possibly related to the interaction between rasagiline and SSRI/SNRIs.

During the 2009-2010 PSUR period, there were three reports of overdosing, all involved ingestion of 2 mg rasagiline per day either as a single dose or 1 mg twice in a day. No adverse events were experienced. There was one report of medication abuse involving rasagiline and several other drugs related to the patients underlying psychological condition. One reported pregnancy was discontinued after a few days.

Since PD occurs in an aging population, evaluation of the elderly aged over 80 years was undertaken. There were 51 confirmed reports in this age group, 29 serious and 22 non-serious. The only event that occurred in more than one subject was fall (n=2). All reported events were as expected in an elderly group.

One case of off label use was reported. In this case rasagiline was used to treat tremor but it was discontinued after one week due to the side-effects experienced. There were no reports concerning events occurring in patients with either renal or liver impairment. At the time of this evaluation, there had been no reports of long-term treatment with rasagiline published[7]. Three cases of medication error have been described (described as overdoses; see above). There were three deaths reported for which there was limited information despite considerable follow-up efforts. No conclusions as to the role of rasagiline in these deaths could therefore be made.

Evaluator's overall conclusions on clinical safety

The methodology used to evaluate the safety and tolerability of rasagiline in Study **TVP-1012-500** was appropriate. The findings are in keeping with the established safety profile of

[6]A measure of the extrinsic pathway of coagulation used to determine the clotting tendency of blood.

[7] Two studies have since been published:
(1) Lew MF *et al* (2010). Long-Term Efficacy of Rasagiline in Early Parkinson's Disease. *Int J Neurosci* 120(6):404-408 and (2) Hauser RA, Lew MF *et al.* (2009). Long-term Outcome of Early Versus Delayed. Rasagiline Treatment in Early Parkinson's Disease. Movement Disorders. 24(4): 564-573

rasagiline. There were no new safety signals from Study **TVP-1012-500** and there was no evidence of dose related effects for any of the adverse events. There was evidence of an increase in some of the biochemistry and haematology variables following treatment with 2 mg rasagiline but these were considered not clinically significant.

The ISS found that overall, an increase in drug exposure duration of 64% from January 2006 to January 2009 has not altered the profile of common, cardiovascular and neuropsychiatric AEs, SAEs and DAEs from that previously documented. Safety data was also obtained from the latest PSUR and no new safety signals were detected. There were non-fatal reported cases of overdoses, tyramine interactions and serotonin syndrome from post marketing studies, which were not seen during the clinical development program but were considered to be in line with the known characteristics of rasagiline. No changes to the CCDS (edition 3, 2009) were thought necessary.

Several relevant published references related to clinical safety and the association between PD and melanoma were included with the current Australian submission. The incidence of melanoma during Study **TVP-1012-500** was much lower (one case representing a rate of 0.9 subjects per 1000 patient years of rasagiline treatment) than during the previous clinical studies (6.7 subjects per 1000 patient years of rasagiline treatment and 4.5 subjects per 1000 patient years of PBO treatment). The major reason for this discrepancy is that dermatological screening was carried out prior to Study **TVP-1012-500** and those subjects who had a melanoma or a history of melanoma or pre-existing suspicious skin lesions who would not agree to biopsy were excluded from participating. In the earlier studies, such screening was introduced about halfway through the program due to the frequency of melanomas diagnosed.

The literature data submitted by the sponsor was updated by a Medline search of the terms "melanoma" and "Parkinson's Disease". There have now been large studies from several countries including Denmark, the USA, the UK and Israel (Olsen *et al* 2005, 2006, 2007, Driver *et al* 2007, Becker *et al* 2010, Bertoni *et al* 2010 and Inzelberg *et al* 2011) which have all found that melanoma is more prevalent in PD patients than in the general population. Two studies have also found a higher incidence of PD in melanoma subjects; one from the USA (Rigel *et al* 2006) and one from Australia (Baade *et al* 2007). It was thought that the increase in melanoma rates might be related to treatment with levodopa but several studies have found an increased incidence of melanoma even before diagnosis of PD (Olsen *et al* 2006, 2007, Schwid *et al* 2010, Bertoni *et al* 2010 and Inzelberg *et al* 2011). Whether this link between melanoma and PD is due to genetic (Gao *et al* 2009) or environmental factors (Olsen *et al* 2011) is not yet clear but may be associated with pigmentation changes in melanin and/or melanin synthesis enzyme, genetic correlations or autophagy deficits (Pan *et al* 2011).

Clinical Summary and Conclusions

Studies **TVP-1012/432**, **TVP-1012-120-TYR** and **TQT-TVP-1012-121** investigated the PK of rasagiline following doses of 1, 2, and 6 mg. Dose proportionality was demonstrated for C_{max} but non linearity was observed for AUC with increasing dose. In addition, the elimination half-life increased with increasing doses. This appears to be a result of undetectable plasma rasagiline concentrations hours after dosing with the lower 1 and 2 mg doses. A biphasic elimination and plasma trough levels were largely only detectable after 6 mg doses. Thus the half-life of 1 mg may be underestimated; however this is of academic interest as the dosage recommended is once daily and the higher doses are not to be licensed. It does not impinge on the other findings of these studies which included no effects of age or gender on rasagiline pharmacokinetics, and no interaction between rasagiline and LD/CD. Subjects with moderate levels of renal impairment had comparable plasma exposure to the healthy controls. Thus, no dosage adjustments are required for the elderly or those with moderate renal impairment.

The PD Study **TVP-1012-120-TYR** showed the selectivity of 1 mg rasagiline for MAO-B and confirmed that a low tyramine diet is not required for the proposed dose. Study **TQT-TVP-**

1012-121 did not find any effects of rasagiline on cardiac repolarisation as assessed by QTc prolongation. There were no new safety issues from the PK/PD studies.

The focus of the current Australian submission was on safety and no further clinical efficacy studies were submitted. One new clinical safety study was submitted, Study **TVP-1012-500**. No new safety concerns were identified in this study. There were non-fatal reported cases of overdoses, tyramine interactions, and serotonin syndrome from post marketing studies which were not seen during the clinical development program but these are in line with the known characteristics of rasagiline. The current data on melanoma will be discussed below.

Benefit risk assessment

Benefits

Current treatments for PD, most commonly levodopa, ameliorate symptoms but do not slow the clinical progression of the disease. However, side-effects particularly dystonia and dyskinesias may develop and worsen over time. Hence, there is a need for more effective drugs to treat this condition. Rasagiline is a selective, irreversible MAO-B inhibitor which increases nigrostriatal dopamine concentrations. The efficacy for rasagiline as monotherapy or as adjunctive treatment to levodopa was established in the previous Australian submission. Rasagiline has been approved for marketing in Europe (February 2005), the USA (May 2006), Canada (August 2006) and numerous other countries to date. The recent Study **TYP-1012-500** suggests that rasagiline may have the ability to slow the progression of the disease (Olanow *et al* 2009) but it has not been approved for this indication to date.

Risks

The risk of development of melanoma was the major concern raised in the previous Australian application. This is considered to be particularly worrying in Australia due to the high background incidence of melanoma in this country. The age-standardised incidence rate for Australia in 2007 was 46.7 per 100,000 of population (Australian Institute of Health and Welfare website[8]). The rate of melanoma in the more recent rasagiline studies was much lower than reported previously due to the inclusion of pre-screening for skin lesions. Several large studies have since shown that melanoma does not appear to be a specific risk for rasagiline but for PD in general and the recommendation for regular skin examinations as detailed in the PI is warranted.

The sponsor's Risk Management Plan (RMP) identified important risks as hallucinations, orthostatic hypotension, malignant melanoma, interaction with antidepressants and a potential risk as interaction with tyramine-containing foods. The Pharmacovigilance Plan (PVP) details collection and processing of adverse drug reaction reports from worldwide sources, PSURs and monthly signal detection meetings. The above identified risks/potential risks will be monitored and included in PSURs. At present, none of these adverse events occur frequently and the RMP/PPV monitoring will detect any changes. In addition, the sponsors have undertaken to carry out a registry-based study (**TVP-1012/401)** to determine the incidence of melanoma in rasagiline and non-rasagiline treated PD subjects and to compare these to the population in general.

Balance

Total exposure to rasagiline in clinical trials is now more than 4000 patient years. More than 250,000 patient years is estimated from global marketing estimates just for the latest PSUR. No unexpected safety signals have arisen since the launch of the product in Europe in 2005. About half the clinical subjects were >65 years and no significant differences in safety parameters were found in this population which is of particular relevance for PD. The risks outlined in the

[8] http://www.aihw.gov.au/

RMP are important but do not occur frequently, particularly not at the 1 mg dose level. Use of doses higher than 1 mg (as is sometimes done) may lead to increased harms such as tyramine interactions due to loss of selectivity for MAO-B and is therefore not recommended.

Conclusions

Efficacy was shown for the proposed indication in the previous Australian submission. Safety and tolerability have been demonstrated since its launch 2005 with no new safety signals despite the increase in exposure to over 250,000 patient years. It was concluded that rasagiline has a positive risk-benefit ratio and should be registered for the above indication.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

Safety Specification

A summary of the Ongoing Safety Concerns and the planned pharmacovigilance activities as specified by the sponsor are shown in Table 7.

Table 7. Summary of safety concerns and planned pharmacovigilance for Azilect

Important Identified risks:	**Planned actions**
Hallucinations	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR.
Orthostatic hypotension	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR.
Melanoma	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR. Conduct the registry-based study: TVP-1012/401: Risk of melanoma among Parkinson's disease patients.
Interaction with antidepressants including SSRIs/SNRIs and tricyclic antidepressants	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR.
Important Potential risks:	
Interaction with tyramine-containing foods	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR.

Routine pharmacovigilance activities are described in the RMP as:

- collection and processing of adverse drug reaction reports from worldwide sources (healthcare professionals, regulatory authorities, patients/consumers, scientific literature, clinical trials (if any), licence partners etc.)
- expedited and Periodic Safety Update Reports of adverse drug reaction reports to regulatory authorities in the timelines, format and frequencies as described in Volume 9A
- regular (monthly) signal detection meetings.

The sponsor proposes to undertake routine and additional pharmacovigilance activities in relation to the ongoing safety concerns for Azilect.

Summary of Recommendations

It was recommended to the Delegate that the sponsor:

- provide details of the two additional follow-up measures in relation to melanoma that were requested upon approval by the European medicines Agency (EMA) and that have been completed.
- comment on the change in the proposed study design to assess melanoma risk.
- add non-melanoma skin cancer as an ongoing safety concern or justify why it is not an ongoing safety concern.
- comment on the generalisability of the results of Study TVP-1012/401 to patients in Australia.
- commit to an early start date for Study TVP-1012/401.
- with regard to the possible association between Parkinson's disease and skin cancer (not exclusively melanoma), comment on whether taking Azilect is anticipated to further increase the risk of skin cancer in Parkinson's disease patients in Australia and how this risk will be evaluated.
- amend the proposed study protocol for Study TVP-1012/401 to include, as a study objective, the assessment of the risk of non-melanoma skin cancer in the study cohorts or justify why this is not necessary.
- clarify why the proposed Australian PI does not include a precaution regarding eating foods high in tyramine.
- justify why the statement included in the EU, US and Canadian product information documents regarding rare cases of hypertensive crisis associated with the ingestion of unknown amounts of tyramine-rich foods in patients taking rasagiline is not in the proposed Australian PI.
- clarify why the difference between the proposed Australian PI for Azilect and the US and Canadian PI documents with regard to the dose adjustment recommendations in patients with renal impairment.
- clarify why the Australian PI lacks a statement that patients taking Azilect should not undergo surgery requiring general anaesthesia.
- clarify why Azilect is not contraindicated in patients with pheochromocytoma.
- provide comment on the implications of the exclusion of patients with severe hypertension, and hypertension that is not controlled, from the pivotal clinical studies.
- clarify why the proposed PI and CMI do not include reference to SNRIs in view of the important identified risk being defined as "interaction with antidepressants including SSRIs/SNRIs and tricyclic antidepressants".
- clarify why the proposed CMI does not include reference to hallucinations.

It is also suggested to the Delegate that:

- pending the clarification of the relationships between Parkinson's disease, its treatment and melanoma, the sponsor is requested to consider the following risk minimisation activities:

- screening of patients, by a dermatologist or other appropriately qualified health care professional, prior to initiation of treatment with Azilect, involving a skin examination and assessment of risk factors for melanoma
- ongoing periodic skin examination of patients by a dermatologist or other appropriately qualified health care professional
- restriction of the use of Azilect to patients who do not have a history of melanoma and patients who are not at increased risk of melanoma
- inclusion of a statement in the PI, and a consistent statement in the CMI, recommending that the patient is advised to seek immediate medical review if a new or changing skin lesion is identified between periodic skin examinations.

Following the initial review of the RMP by the OPR the sponsor submitted responses to the issues raised and a summary of the proposed post market study (evaluation of the relative risks of melanoma and non-melanoma skin cancers in patients receiving rasagiline versus other treatments for Parkinson's disease) and these were considered acceptable by the OPR evaluator.

The sponsor also agreed with the OPR's recommendation that expert advice be sought from the Australasian College of Dermatologists to identify any further pertinent information that should be collected in Australia with regard to the structured questionnaire that has been developed as an enhanced pharmacovigilance data gathering tool for suspected spontaneous reports of melanoma.

The sponsor agreed to a number of safety related product information changes. These primarily related to additional advice about monitoring for skin lesions, a statement about post market reports of serotonin syndrome, the addition of 'dyskinesia' and 'accidental injury (primarily falls)' to the tabulated *Treatment emergent adverse events* as these are identified within the CCDS, and language about hypertension and rare cases of tyramine-rich food related hypertensive crises in the '*post marketing*' subsection of the '*adverse reactions*' section.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator has provided comments on significant quality changes that have been made since the previous submission. The submission was not re-presented to the Pharmaceutical Sub Committee (PSC) and there are no quality issues which would preclude registration.

Nonclinical

There were no nonclinical objections to registration. New nonclinical data consisting of a safety pharmacology study, a reproductive toxicity study, three analytical development studies and published literature references were submitted for evaluation with this re-submission.

The nonclinical evaluator considered that these additional data had no impact on the conclusions or recommendations of the initial nonclinical evaluation report to the initial submission.

Clinical

Pharmacology

Two pharmacokinetic and two pharmacodynamic studies were submitted. Rasagiline in the range of 1-6 mg had a more than dose proportional increase in AUC. C_{max} however increased in a dose proportional manner. In subjects with moderate renal impairment (creatinine clearance (CL_{cr}) of 30 ≤ 50 mL/min) exposure to rasagiline (assessed as AUC) at the proposed dose of 1 mg daily was similar that of healthy control subjects. However, the AUC for the inactive

metabolite, aminoindan was 1.5 fold higher in the renally impaired. Rasagiline, at doses of up to 6 mg daily, was not associated with ECG changes including changes in the QT interval.

Study TVP-1012-120-TYR examined tyramine sensitivity when administered with rasagiline and also the selectivity of rasagiline for MAO-B. Rasagiline doses up to 6 mg daily were examined. This study showed that the selectivity of rasagiline for MAO-B was lost with doses greater than 2 mg/day.

Safety

TVP-1012-500 (ADAGIO) was a double blind, randomised placebo controlled study to assess the ability of rasagiline therapy to slow clinical progression in subjects with early Parkinson's disease. The study had two phases: a 36-week placebo controlled phase and a 36 week active treatment phase. There were four study groups: those given 1 mg rasagiline daily starting after the 36 weeks of placebo control (Group 1) or starting immediately (Group 2); or 2 mg rasagiline daily starting after 36 weeks placebo control (Group 3) or starting immediately (Group 4). Patients had a recent diagnosis of PD (disease duration of < 18 months and not requiring PD treatment at enrolment or expected to require treatment for the next 9 months). Subjects with melanoma, a history of melanoma or refusal to undergo biopsy of suspicious lesions at screening were excluded. Only safety data from this study were presented.

A total of 1176 subjects were randomised with 1091 entering Phase 1 and 954 completing Phase 2. The mean age was 62 across all four groups (range 31 – 81 across the study). The safety results of most concern were those for melanoma incidence. Subjects underwent skin examinations at screening and during Weeks 36 and 72 or at an early termination visit. During the placebo controlled phase, 558 (96%) of patients given rasagiline had at least one post-baseline skin examination and 36 (6.5%) underwent at least 1 skin biopsy. This can be compared to 568 (96%) placebo subjects having at least one skin examination and 39 (6.9%) having at least one skin biopsy. In the active treatment Phase, 1053 (96.5%) subjects had at least one skin examination and 58 (5.5%) subjects underwent at least one skin biopsy.

In this study, there were 1070.5 patient-years exposure to rasagiline during which one patient given rasagiline was diagnosed with melanoma. This can be compared to 361.5 patient years exposure to placebo during which no patients were diagnosed with melanoma. The patient with melanoma was a 75 years old, from the USA, with fair skin, freckles, a history of multiple seborrheic keratoses and multiple melanocytic naevi. The melanoma was identified at the Week 72 visit when the patient underwent three skin biopsies which identified a squamous cell carcinoma (SCC) at the hairline, a melanocytic nevus on the left leg and a melanoma on the left upper back.

That ISS included data from 15 clinical trials that comprised the original clinical development program for rasagiline as a symptomatic treatment of PD. A total of 1361 PD patients were exposed to rasagiline with 3276.9 patient years exposure accumulated. Of the 1361 patients treated with rasagiline in that program, 22 were diagnosed with malignant melanoma while being treated with rasagiline (6.7 subjects/1000 patient years) compared with 4.5 subjects/1000 patient years for patients given placebo in the same studies and 0.9 patients/1000 patient years in Study TVP-1012-500. The sponsor proposed that this difference was most likely due to the commencement of periodic skin examinations part way through the development program. Of the 22 subjects diagnosed with melanoma in the earlier studies only one had a baseline skin examination. Therefore, the total incidence of melanoma in patients taking rasagiline may have been due to a combination of new and existing cases.

Post-marketing data relevant to melanoma incidence were also presented in the seventh PSUR covering 2009. Three cases of melanoma have been reported in the entire post-marketing period of rasagiline. This represents 1.1 cases/100 000 patient years exposure. This is clearly under-reported compared with the clinical trial incidence.

Risk Management Plan

A RMP was evaluated by the TGA. Following some modifications by the sponsor, the RMP is now considered acceptable. The RMP has been modified to include changes to the PI. A request was made that the sponsor seek expert advice from the Australasian College of Dermatologists to identify any further pertinent information that should be collected in Australia with regard to the structured questionnaire that has been developed as an enhanced pharmacovigilance data gathering tool for suspected spontaneous reports of melanoma. The sponsor was requested to submit a timeframe and commitment for reporting of the outcome of this consultative process to the TGA.

The sponsor in the USA, Teva Neuroscience, proposed to evaluate the relative risk of melanoma in patients receiving Azilect or other PD treatments in a retrospective cohort study using multiple large automated claims databases as the data source. The FDA has agreed to this. Due to variations in the background rates of melanomas, the FDA recommended that North American and non-North American patients be analysed separately. Reporting of this study is anticipated by early 2013.

Risk-Benefit Analysis

Delegate Considerations

No correlation of the pharmacokinetics of rasagiline with its pharmacological effect was demonstrated and none was expected because rasagiline irreversibly inhibits MAO-B. Therefore, the demonstrated lack of a linear relationship between dose and AUC is not clinically relevant. No dose adjustment is required in patients with mild to moderate renal impairment. The loss of MAO-B selectivity with higher doses of rasagiline strongly indicates that the proposed dose should not be exceeded and that patients at risk of higher exposures, for example due to hepatic impairment, should not receive rasagiline.

The PK of rasagiline in patients with hepatic impairment was assessed in Study TVP-1012/424 which was evaluated with the previous Australian submission. In that study, subjects with mild hepatic impairment (Child-Pugh Class A[9]) had a mean 15% increase in C_{max} and a mean 35% increase in AUC relative to healthy control subjects. The sponsor has accepted that patients with any degree of hepatic impairment should not receive rasagiline.

The Delegate did note that the FDA permits a 0.5 mg/day dose for patients with mild hepatic impairment. (Child-Pugh score 5-6).

The central question of whether rasagiline presents an additional risk of malignant melanoma in patients with PD has not yet been fully addressed. However it is clear that, at least with treatment for up to 72 weeks, the extent of increased risk, if it exists at all, is very small. The cohort study that will be conducted as part of the postmarket commitment in the USA should answer whether, relative to other treatment options for PD, rasagiline increases the risk of development of malignant melanoma with longer term use. Although this study could not include Australian patients, an analysis of patients who had a higher baseline risk of melanoma would have been particularly useful but difficult to incorporate into the design of the study.[10]

Conclusion and recommendation

The Delegate proposed to register Azilect containing rasagiline mesilate 1 mg for the symptomatic treatment of idiopathic Parkinson's disease (PD) as monotherapy (without

[9] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

[10] The sponsor added the comment that a higher baseline risk is difficult to define since it may be due to genetic, environmental or other factors. A higher risk population could therefore not be identified or defined within the US study.

concomitant levodopa/ decarboxylase inhibitor therapy) or as adjunct therapy (with concomitant levodopa/ decarboxylase inhibitor therapy).

The advice of the Advisory Committee on Prescription Medicines (ACPM) was particularly requested on whether the post-market commitments agreed to by the sponsor are adequate to address the question of whether, and to what extent, rasagiline increases the risk of development of malignant melanoma in patients with Parkinson's disease.

Response from Sponsor

The sponsor advised that they had no comments to make on the quality or nonclinical evaluation reports.

In regard to the clinical evaluation report, the sponsor agreed with the findings of the Delegate. The Delegate requested that Lundbeck seek the opinion of the Australasian College of Dermatologists to identify any further pertinent information that should be collected in Australia. The sponsor advised that the Melanoma Questionnaire has been submitted to a specialist in the field and the questionnaire was being reviewed. The sponsor has reported the findings and provided a revised questionnaire.

The latest Periodic Safety Update Report (eighth edition), covering the period 3 January2010 to 2 January2011 has been provided to the TGA. A summary tabulation of serious adverse events not previously submitted to the TGA and which do not appear in the proposed PI was also submitted to the TGA (covering the period from 3 January 2011 to 4 May 2011). There were no new safety signals reported in the most recent PSUR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Lundbeck Australia Pty Ltd to register the new chemical entity rasagiline mesilate (Azilect) tablet 1 mg for the indication:

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).

In making this recommendation, the ACPM confirmed its previous opinion of the 241st meeting that there were no quality, pharmaceutical chemistry or nonclinical concerns and that efficacy had been adequately demonstrated. The grounds for rejection of the application for registration by the original Delegate were based primarily on an apparent increased risk of melanoma in patients treated with rasagiline.

The ACPM agreed with the current Delegate that the question of whether rasagiline presents an additional risk of malignant melanoma in patients with PD has not yet been fully addressed. Nonetheless, the submitted evidence from Study TVP-1012-500 (ADAGIO) does suggest that the risk, from up to 72 weeks exposure to rasagiline at least, is very small.

Despite the reassurance of the now wider post market experience, it was noted that the majority of this experience was in lower melanoma incidence regions and the ACPM was concerned that the higher background rate of melanoma documented in Australia may cause a stronger association between rasagiline and increased melanoma risk than has been apparent to date. It was noted that regular periodic skin reviews are already well covered in the Product Information. It was considered that a robust RMP is necessary and noted that a suitable plan has been developed.

If registered, the specific conditions of registration should include:

- The provision to the TGA at the earliest opportunity of the results and analysis of the post-market safety study in long term treatment to be conducted in the USA.

- The active collection of post-market data on rates of melanoma specifically in Australian patients.
- Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include clearer statements on tyramine interaction.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Azilect rasagiline mesilate 1 mg tablets blister pack and Azilect rasagiline mesilate 1 mg tablet bottle for oral use, indicated for:

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).

Specific Conditions Applying to These Therapeutic Goods include:

The implementation in Australia of the rasagiline mesilate Risk Management Plan (RMP), version 1.0, dated 23 March 2010, included with submission PM-2010-00798-3-1 and any subsequent revisions, as agreed with the TGA and its Office of Product review, with the addition of:

1. Targeted follow up of all melanoma events (in Australia) using the melanoma questionnaire; and
2. Submission of the final TVP-1012/401 study protocol, the pilot study report and the final study report as updates in the PSUR.

Clinical References

Australian Institute of Health and Welfare website: www.aihw.gov.au/acim-books/

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

AZILECT

NAME OF THE DRUG:

Rasagiline mesilate

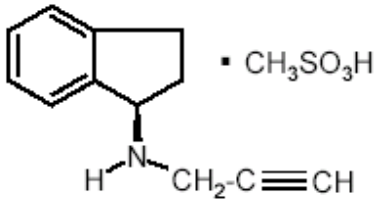
Chemical name
N-propargyl-1(R)-aminoindan mesilate

Chemical Abstracts No.
161735-79-1

Empirical formula
$(C_{12}H_{13}N).\ CH_4SO_3$

Molecular weight
267.34

Structural formula:



DESCRIPTION:

Rasagiline mesilate is a white to off-white powder, freely soluble in water or ethanol and sparingly soluble in isopropanol.

Dissociation Constant: pKa ($R_2NH_2^+/R_2NH$) = 7.4
Partition Coefficient (Log P): Octanol/Water

pH	1.2	5.0	7.0	7.4
Log P	-1.10	0.09	1.56	1.84

Excipients in AZILECT: mannitol, silica - colloidal anhydrous, starch maize, starch - pregelatinised maize, stearic acid and talc – purified.

PHARMACOLOGY:

Pharmacodynamics

In *ex vivo* animal studies in brain, liver and intestinal tissues rasagiline was shown to be a potent, irreversible monoamine oxidase type B (MAO-B) selective inhibitor. In clinical studies rasagiline at the recommended therapeutic dose was also shown to be a potent and irreversible inhibitor of MAO-B in platelets.

Because of rasagiline's selectivity for MAO-B as compared to MAO-A at the recommended clinical dose it will induce significant inhibition of MAO-B only. Aminoindan, a major metabolite, is not a MAO-B inhibitor, but may contribute to rasagiline's effect in experimental models.

The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

It has been shown that, *in vivo* within the human body, there is no bioconversion of rasagiline mesilate (R enantiomer) to its S enantiomer (as determined in plasma samples for healthy volunteers dosed with rasagiline).

Pharmacokinetics

Absorption
Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 0.5 hours. The absolute bioavailability of rasagiline after a single oral dose is about 36%. First pass metabolism is responsible for the incomplete bioavailability.

Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the drug is taken with a high fat meal. Because AUC is not significantly affected, rasagiline can be administered with or without food.

Distribution
The mean volume of distribution following a single i.v. dose is 243 L indicating that there is significant tissue uptake of rasagiline. *In vitro* plasma protein binding ranges from 88-94% with mean extent of binding of 61-63% to human albumin over the concentration range of 1-100 ng/ml.

Metabolism
Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield: 1-aminoindan, 3-hydroxy-N-propargyl-1-aminoindan and 3-hydroxy-1-aminoindan. *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on cytochrome P450 (CYP) system, with CYP 1A2 being the major isoenzyme

involved in rasagiline metabolism. Conjugation of rasagiline and its metabolites was also found to be a major elimination pathway to yield glucuronides.

Excretion
After oral administration of ^{14}C-labelled rasagiline, elimination of radioactive material occurred primarily via urine (62.6 %) and secondarily via faeces (21.8 %), with a total recovery of 84.4 % of the dose over a period of 38 days. Less than 1 % of rasagiline is excreted as unchanged drug in urine.

Linearity/non-linearity
Rasagiline pharmacokinetics are linear for Cmax but show a more than proportional increase in AUC for the 1-2 mg dose range. Its terminal half-life is 0.6-2 hours for the 1 mg dose and longer for higher doses, but there is no correlation with its pharmacological effect due to irreversible inhibition of MAO-B.

Elderly patients
Population pharmacokinetics analysis in early PD patients on rasagiline monotherapy (n=352) indicates that a decrease in oral clearance is associated with increasing age (e.g. a 30 % decrease in clearance as age increases from 32 to 79 years). Specific studies with elderly subjects have shown that there is no effect of age on rasagiline's pharmacokinetics either as monotherapy or as adjunct to levodopa. Rasagiline was well-tolerated in elderly PD patients in both monotherapy and adjunct therapy and no dosage adjustments are required for the elderly.

Children and adolescents (<18 years)
Rasagiline has not been investigated in patients below 18 years of age.

Gender
The pharmacokinetic profile of rasagiline is similar in men and women.

Patients with hepatic impairment

Following repeat dose administration (7 days) of rasagiline (1mg/day) in subjects with mild hepatic impairment (Child-Pugh score 5-6), AUC and C_{max} were increased by 2 fold and 1.4 fold, respectively, compared to healthy subjects. In subjects with moderate hepatic impairment (Child-Pugh score 7-9), AUC and C_{max} were increased by 7 fold and 2 fold, respectively, compared to healthy subjects (see CONTRAINDICATIONS).

Patients with renal impairment
Following repeat dose administration (7 days) of rasagiline (1mg/day) in subjects with mild renal impairment (CLcr 50-80 mL/min), slightly higher AUC was observed, while C_{max} was unchanged. In subjects with moderate renal impairment (CLcr 30-49 mL/min), a lower C_{max} (44 %) and AUC (17 %) compared to healthy subjects was observed. An additional study in moderately renal impaired patients demonstrated similar results. Since impaired renal function has little influence on rasagiline pharmacokinetics, it can be administered at the recommended dose to subjects with moderate renal impairment.

CLINICAL TRIALS:

The efficacy of rasagiline was established in three randomized, placebo-controlled trials. In one of these trials rasagiline was given as initial monotherapy treatment in study and in the other two as adjunct therapy to levodopa.

Monotherapy

In the monotherapy trial (TEMPO), 404 patients were randomly assigned to receive placebo (138 patients), rasagiline 1mg/day (134 patients) or rasagiline 2 mg/day (132 patients) and were treated for 26 weeks. The average duration of Parkinson's disease in patients in this trial was 1 year (range 0-11years). Patients were not allowed to take levodopa, dopamine agonists, selegiline, amantadine, but if necessary, could take stable doses of anticholinergic medication. The primary analysis was in the intention-to-treat (ITT) population.

In this study, the primary measure of efficacy was the change from baseline in the total score of the Unified Parkinson's Disease Rating Scale [UPDRS, Parts I-III: mentation (Part I) + activities of daily living (ADL) (Part II) + motor function (Part III)]. The UPDRS is a multi-item rating scale that measures the ability of a patient to perform mental and motor tasks as well as activities of daily living. A reduction in the score represents improvement and a beneficial change from baseline appears as a negative number.

In the primary measure of efficacy the difference between the mean change from baseline to week 26/termination (LOCF) was statistically significant for rasagiline 1 mg compared to placebo (-4.2, 95% CI [-5.7, -2.7]; p<0.0001) and for rasagiline 2 mg compared to placebo (-3.6, 95% CI [-5.0, -2.1]; p<0.0001). The efficacy of rasagiline 1 mg and 2 mg was comparable.

Table 1 displays the results of the trial.

Table 1. Parkinson's disease Patients receiving rasagiline as monotherapy (TEMPO)

Primary Measure of Efficacy: ***Change in total UPDRS score***				
	Baseline score	Change from baseline to termination score	95% [CI]	p-value vs. placebo
Placebo	24.5	4.07	[3.04 , 5.10]	---
1.0 mg/day	24.7	-0.13	[-1.16 , 0.91]	< 0.0001
2.0 mg/day	25.9	0.51	[-0.55 , 1.57]	< 0.0001

Adjunct therapy

Patients had Parkinson's disease for an average of 9 years (range 5 months to 33 years) in both studies, had been taking levodopa for an average of 8 years (range 5 months to 32 years), and had been experiencing motor fluctuations for approximately 3 to 4 years (range 1 month to 23 years). Patients were also allowed to take stable doses of additional anti-PD

medications at entry into the trials. In both trials, approximately 65% of patients were on dopamine agonists and in the North American study approximately 35% were on entacapone. The primary analysis was in the intention to treat (ITT) population.

In both trials the primary measure of efficacy was the change from baseline to the end of the treatment period in the mean number of hours that were spent in the “OFF” state during the day (determined from “24-hour” home diaries completed for 3 days prior to each of the assessment visits). The secondary measures of efficacy included global assessments of improvement by the examiner, ADL subscale scores when OFF and UPDRS motor while ON.

In the first trial (LARGO), patients were randomly assigned to receive placebo (229 patients), or rasagiline 1 mg/day (231 patients) or the COMT inhibitor, entacapone, 200 mg taken along with scheduled doses of levodopa/decarboxylase inhibitor (227 patients), and were treated for 18 weeks. Patients averaged approximately 5.6 hours daily in the “OFF” state at baseline as confirmed by home diaries and were taking 3 to 10 daily doses of levodopa/decarboxylase inhibitor. In the analysis of the measures of efficacy there was no direct comparison between rasagiline and entacapone; rasagiline 1mg/day and entacapone with each levodopa dose were each separately compared to placebo. The comparison between entacapone and placebo serves for validation and exploratory purposes.

In the second trial (PRESTO), patients were randomly assigned to receive placebo (159 patients), rasagiline 0.5 mg/day (164 patients) or rasagiline 1 mg/day (149 patients), and were treated for 26 weeks. Patients averaged approximately 6 hours daily in the “OFF” state at baseline, as confirmed by home diaries.

In LARGO, the mean difference in the number of hours spent in the “OFF” state compared to placebo was -0.78h, 95% CI [-1.18, -0.39h], p=0.0001. The mean total daily decrease in the OFF time was similar in the entacapone group (-0.80h, 95% CI [-1.20, -0.41], p<0.0001) to that observed in the rasagiline 1 mg group. In PRESTO, the mean difference compared to placebo was -0.94h, 95% CI [-1.36, -0.51], p<0.0001. There was also a statistically significant improvement over placebo with the rasagiline 0.5 mg group, yet the magnitude of improvement was lower.

The observed decrease in total daily OFF time were accounted for by an increase in total daily ON time (adjusted mean difference 0.86 h, 95% CI [0.47, 1.26] for rasagiline 1 mg vs. placebo in the first trial, 1.02h 95% CI [0.59, 1.46] in the second trial). This was predominantly found to be for "good" ON ("ON1") time, with a similar magnitude of improvement between studies (0.81h, 95% CI [0.36, 1.27] for LARGO, 0.78h, 95% CI [0.26, 1.31] for PRESTO). In LARGO, there was almost no change in the amount of "troublesome" ON (“ON2”) compared with baseline (adjusted mean difference vs. placebo 0.09h, 95% CI [-0.28, 0.46], p=0.6209). In PRESTO, "ON2" time increased slightly but significantly for rasagiline 1 mg (adjusted mean difference vs. placebo 0.37 h [95% CI 0.00, 0.74] p= 0.0479), though was almost unchanged for rasagiline 0.5 mg. In these studies the change in levodopa dose was allowed only in the first six weeks of treatment.

Tables 2 and 3 below display the results of the two studies:

Table 2 Parkinson's disease Patients Receiving AZILECT as Adjunct Therapy (LARGO)[1]

Primary Measure of Efficacy: ***Change in mean total daily "OFF" time***				
	Baseline (hours)	Change from baseline to treatment period (hours)	95% [CI]	p-value vs. placebo
Placebo	5.54	-0.40	[-0.69 , -0.10]	---
1.0 mg/day	5.58	-1.18	[-1.47 , -0.88]	0.0001
Entacapone, 200 mg/LD dose	5.58	-1.20	[-1.49 , -0.90]	<0.0001
Secondary Measures of Efficacy				
	Baseline	Change from baseline to termination score	95% [CI]	p-value vs. placebo
Global Improvement score, rated by the Examiner				
Placebo	---	-0.37	[-0.51 , -0.23]	---
1.0 mg/day	---	-0.86	[-1.00 , -0.72]	< 0.0001
Entacapone, 200 mg/LD dose	---	-0.72	[-0.86 , -0.59]	0.0002
UPDRS ADL (Activities of Daily Living) subscale score while "OFF"				
Placebo	18.8	-0.63	[-1.22 , -0.05]	---
1.0 mg/day	18.9	-2.34	[-2.92 ,-1.76]	< 0.0001
Entacapone, 200 mg/LD dose	19.0	-2.01	[-2.59 , -1.44]	0.0006
UPDRS Motor subscale score while "ON"				
Placebo	23.7	-0.48	[-1.48 , 0.53]	---
1.0 mg/day	23.7	-3.41	[-4.41 , -2.42]	< 0.0001
Entacapone, 200 mg/LD dose	23.0	-3.21	[-4.20 , -2.21]	< 0.0001

[1] the results for each group are relative to placebo; there is no direct comparison between rasagiline and entacapone

Table 3 Parkinson's Disease Patients Receiving AZILECT as Adjunct Therapy (PRESTO)

Primary Measure of Efficacy: ***Change in mean total daily "OFF" time***				
	Baseline (hours)	Change from baseline to treatment period (hours)	[CI]	p-value vs. placebo
Placebo	6.0	-0.91	[-1.22 , -0.60]	---
0.5 mg/day	6.0	-1.41	[-1.70 , -1.11]	0.0199
1.0 mg/day	6.3	-1.85	[-2.16 , -1.53]	< 0.0001
Secondary Measures of Efficacy				
	Baseline (score)	Change from baseline to termination score	[CI]	p-value vs. placebo
Global Improvement score, rated by the Examiner				
Placebo	---	-0.02	[-0.21 , 0.16]	---
0.5 mg/day	---	-0.41	[-0.59 , -0.22]	0.0027
1.0 mg/day	---	-0.70	[-0.89 , -0.51]	< 0.0001
UPDRS ADL (Activities of Daily Living) subscale score while "OFF"				
Placebo	15.5	0.78	[0.13 , 1.43]	---
0.5 mg/day	15.7	-0.42	[-1.06 , 0.21]	0.0075
1.0 mg/day	15.6	-0.56	[-1.22 , 0.11]	0.0040
UPDRS Motor subscale score while "ON"				
Placebo	20.8	1.89	[0.68 , 3.10]	---
0.5 mg/day	21.4	-1.02	[-2.18 , 0.14]	0.0007
1.0 mg/day	21.0	-0.98	[-2.19 , 0.23]	0.0011

INDICATIONS:

AZILECT is indicated 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).

CONTRAINDICATIONS:

Rasagiline is contraindicated for use in patients who have demonstrated hypersensitivity to rasagiline or tablet excipients.

Concomitant treatment with monoamine oxidase inhibitors (MAOIs) should be avoided (see Interactions with other medicines). At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors.

Concomitant treatment with pethidine should be avoided (see Interactions with other medicines). At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with pethidine.

Concomitant treatment with tramadol, tapentadol, methadone, dextropropoxyphene, dextromethorphan and St John's wort should be avoided.

Concomitant administration of rasagiline with ciprofloxacin and other potent CYP1A2 inhibitors should be avoided. (see PRECAUTIONS, Interactions with other medicines).

Hepatic impairment (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

PRECAUTIONS:

Serotonin Syndrome

Severe CNS toxicity associated with hyperpyrexia has been reported with the combined treatment of an antidepressant e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, tetracyclic antidepressants, and a non-selective MAOI (e.g. phenelzine, tranylcypromine) or selective MAO-B inhibitors, such as selegiline and rasagiline (AZILECT). These adverse reactions are often described as 'serotonin syndrome' which can result in death. In the postmarketing period, non-fatal cases of serotonin syndrome have been reported in patients treated with antidepressants concomitantly with AZILECT.

The symptoms of serotonin syndrome have included behavioural and cognitive/mental status changes (e.g. confusion, hypomania, hallucinations, agitation, delirium, headache and coma), autonomic effects (e.g. syncope, shivering, sweating, high fever/hyperthermia, hypertension, tachycardia, nausea, diarrhoea), and somatic effects (e.g. muscular rigidity, myoclonus, muscle twitching, hyperreflexia manifested by clonus and tremor).

Risk for Hypertensive Crisis and Nonselective Monoamine Oxidase Inhibition above the recommended dose

AZILECT is a selective inhibitor of monoamine oxidase (MAO)-B at the recommended doses of 1mg daily. AZILECT should not be used at daily doses exceeding 1mg/day because of the risks of hypertensive crisis and other adverse reactions associated with nonselective inhibition of MAO.

Dietary tyramine restriction is not ordinarily required with ingestion of most foods and beverages that may contain tyramine, during treatment with recommended doses of AZILECT. However, certain foods (e.g., aged cheeses) may contain very high amounts of tyramine and could potentially cause a hypertensive "cheese" reaction in patients taking AZILECT even at the recommended doses due to mild increased sensitivity to tyramine. Patients should be advised to avoid foods (e.g., aged cheese) containing a very large amount of tyramine while taking recommended doses of AZILECT because of the potential for large increases in blood pressure.

Selectivity for inhibiting MAO-B diminishes in a dose-related manner as the dose is progressively increased above the recommended daily doses.

There were no cases of hypertensive crisis in the clinical development program associated with 1 mg daily rasagiline treatment, in which most patients did not follow dietary tyramine restriction. In addition, the results of five tyramine challenge studies in volunteers and PD patients exposed to high to very high doses of dietary tyramine, indicate that rasagiline can ordinarily be used safely without dietary tyramine restrictions.

Very rare cases of hypertensive crisis have been reported in the post-marketing period in patients after ingesting unknown amounts of tyramine-rich foods while taking recommended doses of AZILECT.

Dyskinesia Due to Levodopa Treatment

When used as an adjunct to levodopa, AZILECT may potentiate dopaminergic side effects and may therefore exacerbate pre-existing dyskinesia (dyskinesia occurred in 10.3% of 380 patients treated with 1 mg AZILECT and 6.4% of 388 patients treated with placebo). Decreasing the dose of levodopa may ameliorate this side effect.

Postural Hypotension

Dopaminergic therapy in Parkinson's disease patients has been associated with postural hypotension. When used as monotherapy, postural hypotension was reported as an adverse event in 2.7 % of 149 patients treated with 1 mg AZILECT and 4.6 % of 151 patients treated with placebo. In the monotherapy trial, postural hypotension did not lead to drug discontinuation and premature withdrawal from clinical trials in the AZILECT treated patients or the placebo treated patients. When used as an adjunct to levodopa, postural hypotension was reported as an adverse event in 4.7% of 380 patients treated with 1 mg AZILECT and 1.3% of 388 patients treated with placebo. Postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in 2 (0.5 %) of the AZILECT treated patients, and none of the placebo treated patients.

Clinical trial data suggest that postural hypotension occurs most frequently in the first two months of AZILECT treatment and tends to decrease over time.

Hallucinations

Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. When used as monotherapy, hallucinations were reported as an adverse event in 1.3 % of 149 patients treated with 1 mg AZILECT and in 0.7 % of 151 patients treated with placebo. In the monotherapy trial, hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 2 (1.3 %) of the 1 mg AZILECT treated patients and in none of the placebo treated patients. When used as an adjunct to levodopa, hallucinations were reported as an adverse event in 2.9% of 380 patients treated 1 mg/day AZILECT and 2.1% of 388 patients treated with placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 2 (0.5 %) patients treated with AZILECT 1 mg/day and in 1 (0.3 %) of the placebo treated patients.

Melanoma

During the entire development program, the rate of melanoma in AZILECT treated patients was 7.2 cases/1000 person years (17 melanomas in 2363 person years). After the sixth case of melanoma was detected in the AZILECT development program, subjects in ongoing studies were screened for melanoma through a skin examination every three months, which is likely to have increased the number of melanomas detected. During the placebo-controlled trial portion of the AZILECT development program, melanomas occurred in rasagiline treated subjects at a rate of 11.6 cases/1000 person years (4 melanomas in 344 person years) and in placebo treated subjects at a rate of 4.8 cases/1000 person years (1 melanoma in 210 person years).

For the subjects treated with AZILECT rasagiline, median duration of treatment until melanoma diagnosis was 15.6 months (mean 22.9 months), with a range of 2 to 54 months. Five of the melanomas were in patients who received rasagiline only and 12 were in patients who received rasagiline and levodopa (in most cases also additional dopaminergic therapy). There was no increased incidence of melanomas observed in rasagiline clinical trial with increased extent of exposure over time.

Epidemiologic studies of Parkinson disease patients demonstrate higher rates of melanoma in such patients than in the general population (perhaps 2- to 4-fold higher). In addition, two epidemiological cohort studies that assessed the prevalence of melanoma in PD patients (studies conducted in: North American n = 2106, in which a total of 24 melanomas were detected, prevalence 1.1%, and Israel: n = 1395, in which 10 melanomas were detected, prevalence 0.7% have shown that the prevalence of melanoma in PD patients is substantially higher (as compared to other data sources of the general population).

During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

The relationships between Parkinson's disease, its treatments, and melanoma are not completely understood. Until the melanoma risk associated with Parkinson's disease and/or dopaminergic therapy (including AZILECT) is better understood, it is recommended that Parkinson's disease patients, including those being treated with AZILECT, should undergo periodic examination of the skin.

Patients are advised to seek immediate medical review if a new or changing skin lesion is identified between periodic skin examinations.

Tyramine/rasagiline interaction

MAO in the gastrointestinal tract and liver (primarily type A) is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed

intact, to cause a “hypertensive crisis,” the so-called “cheese reaction”. If large amounts of certain exogenous amines (e.g., from fermented cheese, herring, over-the-counter cough/cold medications) gain access to the systemic circulation because MAO-A has been inhibited, they cause release of noradrenaline which may result in a rise in systemic blood pressure. MAOIs that selectively inhibit MAO-B are largely devoid of the potential to cause tyramine-induced hypertensive crisis.

Results of a special tyramine challenge study indicate that rasagiline is selective for MAO-B at recommended doses and can ordinarily be used without dietary tyramine restriction. However, certain foods (e.g., aged cheeses) may contain very high amounts of tyramine and could potentially cause a hypertensive cheese reaction in patients taking AZILECT due to mild increased sensitivity to tyramine. Patients should be advised to avoid foods (e.g., aged cheese) containing a very large amount of tyramine while taking recommended doses of AZILECT because of the potential for large increases in blood pressure. Selectivity for inhibiting MAO-B diminishes in a doserelated manner as the dose is progressively increased above the recommended daily doses.

There were no cases of hypertensive crisis in the clinical development program associated with 1 mg daily rasagiline treatment, in which most patients did not follow dietary tyramine restriction. Despite the selective inhibition of MAO-B at recommended doses of AZILECT, there have been postmarketing reports of patients who experienced significantly elevated blood pressure (including very rare cases of hypertensive crisis) after ingestion of unknown amounts of tyramine-rich foods while taking recommended doses of AZILECT.

Concomitant illnesses

During the AZILECT development program patients with concomitant illnesses (such as cardiovascular, gastrointestinal) and with new or deteriorating concomitant illnesses were allowed to participate or continue the study.

Interactions with other medicines

MAO Inhibitors*:* Rasagiline should not be administered concomitantly with other MAO inhibitors whether used as antidepressants, for the treatment of Parkinson’s disease, or for any other indication as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crisis (see CONTRAINDICATIONS). At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors

Medicinal and natural products without prescription which have MAOI activity:
Rasagiline should not be administered concomitantly with non-prescription medicines which have MAOI activity (e.g. St. John's Wort) (see CONTRAINDICATIONS).

Pethidine
The concomitant administration of rasagiline and pethidine is contraindicated (see CONTRAINDICATIONS). Serious adverse events have been reported with the concomitant use of pethidine and MAO inhibitors including selective MAO B inhibitors. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with pethidine.

Fluoxetine and fluvoxamine
The concomitant use of the SSRIs fluoxetine and fluvoxamine should be avoided. The concomitant use of rasagiline and fluoxetine should be avoided due to the long pharmacodynamic half-life of rasagiline and the long pharmacokinetic half-lives of fluoxetine and its active metabolite. The concomitant use of rasagiline and fluvoxamine should be avoided as it is also metabolized by CYP1A2. At least five weeks (approximately 5 half-lives) should elapse between discontinuation of fluoxetine and initiation of treatment with rasagiline. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine.

Serotonergic drugs
During the AZILECT development program there were no cases of the serotonin syndrome. Treatment with serotonergic drugs in patients primarily with psychiatric illness, taken alone or in combination with other drugs such as MAOIs, has been uncommonly associated with symptoms of myoclonus, tremor, confusion, restlessness, ataxia and hyperreflexia. While usually short lived, this syndrome can lead to intensive care admissions and is potentially fatal. The occurrence of serotonin syndrome may occur after the use of SSRIs, SNRIs, tricyclic, tetracylic antidepressants, 3-4-methylenedioxy-metamphetamine (MDMA or ecstasy), other 5-HT potentiating agents and the antipsychotic agent clozapine. The treatment of choice is the cessation of the drugs responsible.

Selective serotonin reuptake inhibitors (SSRIs), SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors.
No formal clinical pharmacology studies were conducted with the combination of rasagiline with antidepressants. The use of selected antidepressants was allowed in the Phase III clinical trials and a number of patients treated with rasagiline were concomitantly treated with antidepressants without any reports of CNS toxicity (serotonin syndrome). The following antidepressants and doses were allowed in the rasagiline trials: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily and paroxetine ≤ 30 mg/daily. The total exposure for concomitant antidepressant use was: tricyclics n=115, maximum exposure of 6.2 years; SSRIs/SNRIs n=141, maximum exposure of 5.2 years and trazodone n=45, maximum exposure of 5.8 years. The exposure, both in dose and number of subjects, was not adequate to rule out the possibility of an untoward reaction from combining these agents. Therefore, in view of the MAO inhibitory activity of rasagiline, antidepressants should be administered with caution.

In the post-marketing period, cases of serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus have been reported by patients treated with antidepressants/SSRIs/SNRIs concomitantly with rasagiline.

Dextromethorphan or sympathomimetics medications
The concomitant use of rasagiline and dextromethorphan or sympathomimetics including nasal and oral decongestants and cold remedies is not recommended.

Levodopa
Data from population pharmacokinetics in early PD patients (n=31/352) requiring concomitant levodopa therapy showed there was a small decrease in rasagiline clearance (31 %). Data from the population pharmacokinetics study in patients receiving chronic

levodopa treatment as adjunct therapy to rasagiline (n=276) showed there was no effect of levodopa treatment on rasagiline clearance. In view of the results of these two studies, the true effect of levodopa on rasagiline clearance is not yet known.

Effects of other drugs on the metabolism of rasagiline

In vitro metabolism studies have indicated that cytochrome P450 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of rasagiline. Co-administration of rasagiline and ciprofloxacin (an inhibitor of CYP 1A2) increased the AUC of rasagiline by 83%. Co-administration of rasagiline and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either product. Thus, potent CYP1A2 inhibitors may alter rasagiline plasma levels and the concomitant use with rasagiline 1 mg/day is contraindicated (see CONTRAINDICATIONS).

Concomitant administration of rasagiline and entacapone increased rasagiline oral clearance by 28%.

Effect of rasagiline on other drugs

In vitro studies have shown that rasagiline therapeutic concentrations are not expected to cause any clinically significant interference with substrates of cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A).

Effects of alcohol

No studies on the combined effects of rasagiline and alcohol have been performed. However, because of dopaminergic side effects of rasagiline such as postural hypotension, caution should be urged if patients taking rasagiline do intend to drink alcohol, (postural hypotension was reported as an adverse event in rasagiline patients treated with 1 mg vs. patients treated with placebo in monotherapy in: 2.7% vs. 4.6% and in adjunct therapy in: 4.7% vs. 1.3%).

Effect of smoking

Population pharmacokinetics analysis in early PD patients indicated an increase (30-40%) in rasagiline clearance in smokers (% of smokers in the study: 4.8%). Data from the population pharmacokinetics in patients treated with rasagiline as adjunct therapy to levodopa (% of smokers in the study: 5%) showed no effect of smoking on rasagiline clearance. In view of the results of these two studies, the true effect of smoking on rasagiline clearance is not yet known. There is a possibility that rasagiline plasma levels in smoking patients could be decreased, due to induction of the metabolising enzyme CYP1A2.

Patients with hepatic impairment

Rasagiline plasma concentration may increase (up to 2 and 7 fold) in patients with mild (Child-Pugh score 5-6) and moderate (Child-Pugh score 7-9) insufficiency respectively.

Therefore, rasagiline should not be used in patients with any degree of hepatic insufficiency (see CONTRAINDICATIONS).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Carcinogenicity

Two year oral carcinogenicity studies were conducted in mice at doses of 1, 15 and 45 mg/kg/day, and in rats at doses of 0.3, 1 and 3 mg/kg/day (males) or 0.5, 2, 5 and 17 mg/kg/day (females). In rats there were no increases in tumours; plasma exposures (AUC) at the highest doses were about 80 times (males) and 450 times (females) the anticipated human exposure at the maximum recommended clinical dose (1mg/day). In mice, there was an increase in lung tumours (combined adenomas/carcinomas) at 15 and 45 mg/kg/day in both sexes. Plasma exposures (AUC) at these doses were about 180 times and greater than 470 times the anticipated human exposures at the maximum recommended clinical dose (1mg/day), while exposure at the no-effect dose (1mg/kg/day) was about 5 times anticipated clinical exposure.

The carcinogenic potential of rasagiline administered in combination with levodopa/ carbidopa has not been examined.

Genotoxicity

In the presence of metabolic activation, rasagiline was clastogenic *in vitro* in chromosomal aberration assays in human lymphocytes and in the mouse lymphoma tk assay. Rasagiline was negative in bacterial reverse mutation assays *in vitro* (in the presence and absence of metabolic activation) and *in vivo* assays (unscheduled DNA synthesis assay, mouse micronucleus assay). Rasagiline was also negative in the *in vivo* micronucleus assay in mice when administered in combination with levodopa/carbidopa.

Impairment of fertility

No impairment of mating or fertility was seen in male rats treated prior to and throughout the mating period or in female rats treated from prior to mating through late gestation at oral doses up to 3mg/kg/day (more than 30 times human exposure (AUC) at the maximum recommended dose of 1mg/day). The effect of rasagiline administered in combination with levodopa/carbidopa on mating and fertility has not been examined.

Use in pregnancy

Category B3

No effect on embryofetal development was observed in a combined mating/fertility/embryofetal development study in female rats at oral doses up to 3 mg/kg/day (at least 30 fold anticipated clinical exposure (plasma AUC) at the maximum recommended dose, 1 mg/day).

In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1mg/kg/day) orally from the beginning of organogenesis to weaning, both offspring survival and body weights were reduced at 0.3 and 1 mg/kg/day (at least 10 times anticipated human exposure based on AUC, at 1mg/day); the no-effect dose was 0.1 mg/kg/day (no exposure data). In rabbits administered rasagiline orally during the period of organogenesis, an increased incidence of post-implantation loss (resorption or abortion) and lower fetal body weight were noted at high exposures (about 1000 fold or greater the anticipated human exposure based on AUC at 1mg/day), along with maternotoxicity. The no-adverse-effect exposure (AUC) was greater than 60 fold the anticipated human exposure. No increase in fetal malformations was seen in any of the animal reproductive toxicity studies with rasagiline.

Rasagiline may be given as an adjunct therapy to levodopa/carbidopa treatment. In a study in which pregnant rats were dosed orally with rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day), alone and in combination throughout the organogenesis period, there was an increased incidence of wavy ribs in fetuses from rats treated with 1/80/20 mg/kg/day (approximately 8 times the human exposure to rasagiline at 1mg/day on an AUC basis). The clinical significance of the wavy ribs in rodent fetuses is likely to be low. In a study in which pregnant rabbits were dosed orally during the organogenesis period with rasagiline alone (3 mg/kg/day) or at doses of 0.1, 0.6 and 1.2 mg/kg/day in combination with levodopa/carbidopa 80/20 mg/kg/day, an increase in embryofetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day (7 and 13 times anticipated human systemic exposure (AUC) at 1 mg/day, respectively). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone and to a greater extent when rasagiline (at all doses; 1-13 times the plasma rasagiline AUC at the MRHD) was administered in combination with levodopa/carbidopa. This increase is most likely mediated by elevated levodopa levels.

There are no adequate and well-controlled studies of rasagiline in pregnant women. Because animal reproduction studies are not always predictive of human response, AZILECT should be used during pregnancy only if clearly needed.

Use in lactation

Experimental data indicated that rasagiline inhibits prolactin secretion and, thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk, therefore caution should be exercised when rasagiline is administered to a nursing mother.

ADVERSE REACTIONS

Monotherapy

Table 4 lists treatment emergent adverse events that occurred in ≥ 1 % of patients receiving 1 mg/day rasagiline as monotherapy participating in the double-blind, placebo-controlled trial and were with a higher incidence in the rasagiline treated patients. (rasagiline group n=149, placebo group n=151)

Table 4 Treatment Emergent Adverse Events in rasagiline 1 mg-Treated Monotherapy Patients with incidence of ≥ 1 % and above placebo

System Organ Class & Preferred Term		Rasagiline 1 mg (N=149)	Placebo (N=151)
		% of Patients	% of Patients
Body as a whole	Headache	14.1	11.9
	Flu syndrome	6.0	0.7
	Fever	2.7	1.3
	Malaise	2.0	.
	Neck pain	2.0	.
	Allergic reaction	1.3	0.7
	Hernia	1.3	.
Cardiovascular system	Angina pectoris	1.3	.
	Peripheral vascular disorder	1.3	.
Digestive system	Dyspepsia	6.7	4.0
	Anorexia	1.3	.
	Tooth disorder	1.3	0.7
	Vomiting	1.3	0.7
Haematological and and lymphaticsystems	Ecchymosis	1.3	.
	Leucopenia	1.3	.
Musculoskeletal system	Arthralgia	7.4	4.0
	Arthritis	2.0	0.7
	Joint disorder	1.3	0.7
	Tendon disorder	1.3	.
Nervous system	Dizziness	11.4	10.6
	Depression	5.4	2.0
	Paraesthesia	2.0	1.3
	Vertigo	2.0	0.7
	Hallucinations	1.3	0.7
	Libido decreased	1.3	.
Respiratory system	Pharyngitis	2.7	2.6
	Rhinitis	2.7	1.3
	Asthma	1.3	.
Skin and appendages	Alopecia	1.3	0.7
	Contact dermatitis	1.3	.
	Skin carcinoma	1.3	0.7
	Vesiculobullous rash	1.3	.
Special senses	Conjunctivitis	2.7	0.7
	Otitis media	1.3	.
Urogenital system	Albuminuria	1.3	0.7
	Impotence	1.3	0.7
	Urinary urgency	1.3	.

Other events that occurred at an incidence of <1% of patients receiving rasagiline as monotherapy, and were more frequent than in placebo are listed below within body system categories.

***Body as a whole*:** Abscess, cellulitis, chills, gangrene, infection fungal;

***Cardiovascular system**:*, Cerebrovascular accident, heart arrest, myocardial infarct, pallor, thrombosis, vascular disorder;

***Digestive system*:** Colitis, eructation, gastritis, gastrointestinal disorder, nausea and vomiting, periodontitis;

Haematological and lymphatic systems: Anaemia, eosinophilia, leucocytosis;

***Metabolic and nutritional disorders*:** Hyperlipaemia;

***Musculoskeletal system**:* Tendinous contracture;

***Nervous system*:** Abnormal dreams, dystonia, myoclonus, paranoid reaction;

Skin and appendages: Dry skin, urticaria;

Special senses: Eye haemorrhage, glaucoma;

Urogenital system: Breast neoplasm, breast pain, dysmenorrhoea, prostatic specific antigen increase.

Adjunct Therapy

Table 5 lists treatment emergent adverse events that occurred in ≥ 1 % of patients treated with rasagiline 1 mg/day as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trials and were with a higher incidence in the rasagiline treated patients. (rasagiline group n=380, placebo group n=388)

Table 5 Treatment Emergent Adverse Events in Patients Receiving Rasagiline as Adjunct to Levodopa Therapy with incidence of ≥ 1 % and above placebo

System Organ Class & Preferred Term		Rasagiline 1 mg (N=380)	Placebo (N=388)
		% of Patients	% of Patients
Body as a whole	Accidental injury	8.2	5.2
	Abdominal pain	3.9	1.3
	Pain	3.7	3.4
	Neck pain	1.6	0.5
	Hernia	1.3	0.8
	Cellulitis	1.1	0.5
	Flu syndrome	1.1	0.5
Cardiovascular system	Postural hypotension	4.7	1.3
	Hypotension	2.1	1.8
	AV block first degree	1.1	0.5
Digestive system	Nausea	6.8	5.9
	Constipation	4.2	2.1
	Dry mouth	3.4	1.8
	Vomiting	3.4	1.0
	Dyspepsia	2.9	2.3
	Anorexia	2.1	0.5
Haematological and lymphatic systems	Anaemia	1.3	1.0
	Ecchymosis	1.1	0.8
Metabolic and nutritional disorders	Weight loss	4.2	1.5
Musculoskeletal system	Arthralgia	3.2	1.3
	Tenosynovitis	1.3	.
Nervous system	Dyskinesia	10.3	6.4
	Dizziness	5.3	4.9
	Sleep disorder	5.0	4.1
	Somnolence	3.2	2.3
	Hallucinations	2.9	2.1
	Dystonia	2.4	0.8
	Abnormal dreams	2.1	0.8
	Paraesthesia	1.8	1.5
	Ataxia	1.3	0.3
Respiratory system	Dyspnoea	2.1	1.3
Skin and appendages	Rash	2.6	1.5
	Skin benign neoplasm	1.6	1.3
	Sweating	1.6	0.8
Special senses	Abnormal vision	1.6	0.5
Other	Dyskinesia	10.3	6.4
	Accidental injury (primarily falls)	8.2	5.2

Other events that occurred at an incidence of <1% of patients receiving rasagiline as adjunct to levodopa therapy, and were more frequent than in placebo are listed below within body system categories.

***Body as a whole*:** Cyst, halitosis, Kaposi's sarcoma, sepsis;

***Cardiovascular system*:** Bradycardia, vasodilatation, angina pectoris, arrhythmia, bundle branch block, cerebrovascular accident, pulmonary embolus, AV block complete, AV block second degree, blood pressure fluctuations, cardiovascular disorder, myocardial infarct, palpitation, thrombosis, ventricular arrhythmia, ventricular extrasystoles;

***Digestive system*:** Gastroenteritis, gingivitis, dysphagia, oesophagitis, flatulence, gastritis, intestinal obstruction, faecal impaction, gastrointestinal haemorrhage, liver function tests abnormal, megacolon, mouth ulceration,;

***Endocrine system*:** Goiter;

Haematological and lymphatic system: Leucopenia, megaloblastic anaemia, thrombocytopenia;

Metabolic and nutritional disorders: Weight gain, gout, blood urea nitrogen increased, hyperlipaemia, hyperphosphatemia, hypokalaemia, lactic dehydrogenase increased;

Musculoskeletal system: Leg cramps, bursitis, myositis;

***Nervous system*:** Amnesia, hyperkinesias, speech disorder, spinal stenosis, dysautonomia, libido decreased, meningitis, nystagmus, paranoid reaction, personality disorder;

***Respiratory system*:** Asthma, epistaxis, pneumothorax, rhinitis allergic;

***Skin and appendages*:** Pruritus, herpes simplex, skin melanoma, skin ulcer, alopecia, nail disorder, psoriasis;

***Special senses*:** Eye disorder, blindness, diplopia, vitreous disorder;

***Urogenital system*:** Dysuria, albuminuria, urinary urgency, anuria, bladder carcinoma, dysmenorrhoea, kidney pain, nocturia, testis disorder, urogenital anomaly, vaginal haemorrhage.

Other important adverse events that were reported in clinical studies with rasagiline (of different rasagiline doses or without placebo control) and occurred in very few patients each were: rhabdomyolysis following fall and prolonged immobilization and inappropriate antidiuretic hormone (ADH) secretion. The complicated nature of these cases makes it impossible to determine what role, if any, rasagiline played in the pathogenesis of these conditions.

Post-Marketing Data

In the post-marketing period, cases of elevated blood pressure, including very rare cases of hypertensive crisis associated with ingestion of unknown amounts of tyramine-rich foods, have been reported in patients taking rasagiline.

With MAO inhibitors, there have been reports of drug interactions with the concomitant use of sympathomimetic medicinal products.

In post marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking rasagiline.

DOSAGE AND ADMINISTRATION

Rasagiline should be administered orally, at a dose of 1 mg once daily with or without levodopa/decarboxylase inhibitor therapy. It may be taken with or without food. Clinical trials have demonstrated no efficacy advantage for higher doses of rasagiline.

Change of levodopa dose in adjunct therapy: When rasagiline is used in combination with levodopa, a reduction of the levodopa dosage may be considered based upon individual response.

Elderly patients (>65 years)
No change in dosage is required for elderly patients.
Rasagiline was shown to be well-tolerated in elderly PD patients in both monotherapy and adjunct therapy.

Children and adolescents (<18 years):
Not recommended as the safety and efficacy have not been established in this population.

Patients with hepatic impairment:
Rasagiline should not be used in patients with hepatic insufficiency (see CONTRAINDICATIONS).

Patients with renal impairment:
No change in dosage is required for moderate renal impairment.

OVERDOSAGE:

Symptoms reported following overdose of 3-100mg rasagiline included dysphoria, hypomania, hypertensive crisis and serotonin syndrome.

Rasagiline was well tolerated in a single-dose study in healthy volunteers receiving 20 mg/day and in a ten-day study in healthy volunteers receiving 10 mg/day. Adverse events were mild or moderate and not related to rasagiline treatment. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of rasagiline, there were reports of cardiovascular side effects (including hypertension and postural hypotension), which resolved following treatment discontinuation.

Theoretically, overdose can cause significant inhibition of both MAO-A and MAO-B. Symptoms of overdosage, although not observed with rasagiline during clinical development, may resemble those observed with non-selective MAO inhibitors (MAOIs). Although no cases of overdose have been observed with rasagiline during the clinical development program, the following description of presenting symptoms and clinical course is based upon overdose descriptions of non-selective MAO inhibitors.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

There is no specific antidote. In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

PRESENTATION

Blisters: 10, 30 tablets.
*Bottle**: 30 tablets.

* registered in Australia but not marketed

Description of tablets
White to off-white, round, flat, bevelled tablets, debossed with “GIL” and “1” underneath on one side and plain on the other.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

STORAGE CONDITIONS

Store below 25ºC.

Manufactured by:

Teva Pharmaceutical Industries Ltd

Israel

Distributed and Marketed in Australia by:

Lundbeck Australia Pty Ltd
1 Innovation Rd
North Ryde NSW 2113
Ph: +61 2 8669 1000

Date of TGA approval: 12 September 2011

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Reference/Publication #