PRODUCT INFORMATION

AZILECT

NAME OF THE DRUG:

Rasagiline mesilate

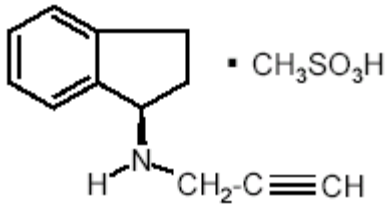
Chemical name
N-propargyl-1(R)-aminoindan mesilate

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.

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes

Rasagiline may cause daytime drowsiness, somnolence, and occasionally (especially if used with other dopaminergic medications), falling asleep during activities of daily living. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with rasagiline. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section “Effects on ability to drive and use machines”).

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.

There have been reports of hypotensive effects when rasagiline is taken concomitantly with levodopa. Patients with Parkinson's disease are particularly vulnerable to the adverse effects of hypotension due to existing gait issues.

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.

Impulse control disorders:

Impulse control disorders (ICDs) can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Similar reports of ICDs have also been received post-marketing with rasagiline. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware of the behavioural symptoms of impulse control disorders that were observed in patients treated with rasagiline, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

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 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. 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

Rasagiline may affect the ability to drive and use machines

Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that rasagiline does not affect them adversely.

Patients being treated with rasagiline and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until they have gained sufficient experience with rasagiline and other dopaminergic medications to gauge whether or not it affects their mental and/or motor performance adversely.

If increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, the patients should not drive or participate in potentially dangerous activities.
Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of rasagiline.

Patients should be cautioned about possible additive effects of sedating medications, alcohol, or other central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants) in combination with rasagiline, or when taking concomitant medications that increase plasma levels of rasagiline (e.g., ciprofloxacin)

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 lymphatic systems	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.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of impulse control disorders has been reported post-marketing with rasagiline, which also included compulsions, obsessive thoughts and impulsive behaviour (see PRECAUTIONS).

Excessive daytime sleepiness (EDS) and sudden sleep onset (SOS) episodes

Excessive daily sleepiness (hypersomnia, lethargy, sedation, sleep attacks, somnolence, and sudden onset of sleep) can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of excessive daily sleepiness has been reported post-marketing with rasagiline.
Cases of patients, treated with rasagiline and other dopaminergic medications, falling asleep while engaged in activities of daily living have been reported. Although many of these patients reported somnolence while on rasagiline with other dopaminergic medications, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported several months after initiation of treatment

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.

Distributed and Marketed in Australia by:

Teva Pharma Australia Pty Ltd
37 Epping Rd
Macquarie Park
NSW 2113
Telephone: 1800 288382

Date of First Inclusion on the ARTG: 06 Feb 2012
Blister (AUST R 170172)
Bottle (AUST R 172457)

Date of most recent amendment: 28 August 2017