

PRODUCT MONOGRAPH

^{Pr}**AZILECT**[®]

(rasagiline mesylate tablets)

**0.5 mg and 1 mg tablets
(as rasagiline mesylate)**

Antiparkinson Agent

Teva Pharmaceutical Industries Ltd.

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PrAZILECT®

(rasagiline mesylate tablets)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	0.5 mg and 1 mg tablets	Colloidal silicon dioxide mannitol, starch, pregelatinized starch, stearic acid and talc

INDICATIONS AND CLINICAL USE

AZILECT (rasagiline mesylate tablets) is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy, and as adjunct therapy to dopamine agonists or to levodopa.

The effectiveness of AZILECT was demonstrated in patients with early Parkinson's disease who were receiving AZILECT as monotherapy and who were not receiving any concomitant dopaminergic therapy. The effectiveness of AZILECT as adjunct therapy was demonstrated in patients with Parkinson's disease who were treated with dopamine agonists in early stages or levodopa in more advanced stages of the disease.

Geriatrics (> 65 years of age):

Approximately half of patients in clinical trials were 65 years and over. There were no significant differences in the safety profile of the geriatric and non-geriatric patients.

Pediatrics (< 18 years of age):

The safety and effectiveness of AZILECT in patients below 18 years of age have not been established.

CONTRAINDICATIONS

Meperidine and Other Analgesics: AZILECT is contraindicated for use with meperidine. Serious, sometimes fatal reactions have been precipitated with concomitant use of meperidine (e.g., Demerol and other tradenames) and MAO inhibitors including selective MAO-B inhibitors. These reactions have been characterized by coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with meperidine.

For similar reasons, AZILECT should not be administered with the analgesic agents tramadol, methadone, tapentadol, and propoxyphene.

Other Drugs: AZILECT should not be used with the antitussive agent dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. AZILECT is also contraindicated for use with St. John's wort, and cyclobenzaprine (a tricyclic muscle relaxant).

MAO inhibitors: AZILECT should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with MAO inhibitors.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Sudden Onset of Sleep

Patients receiving treatment with AZILECT and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on AZILECT, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are not limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician.

Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have

also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

Currently, the precise cause of this event is unknown. It is known that patients with Parkinson's disease experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

AZILECT (rasagiline mesylate) is a selective inhibitor of monoamine oxidase (MAO)-B at recommended doses of 0.5 or 1 mg daily. The selectivity for inhibiting MAO-B diminishes in a dose-related manner as the dose is progressively increased above the recommended daily dose.

AZILECT should not be used at daily doses exceeding those recommended (1 mg/day) because of the risks associated with non-selective inhibition of MAO-B (see ACTION AND CLINICAL PHARMACOLOGY).

Serotonin Syndrome and Antidepressants:

Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combined treatment of an antidepressant (e.g. selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants) and non-selective MAOIs (NARDIL, PARNATE) including the reversible MAOI, moclobemide or selective MAO-B inhibitors, selegiline and rasagiline (AZILECT). These adverse reactions are often described as “serotonin toxicity” or “serotonin syndrome” a potentially serious condition which can result in death. The symptoms of serotonin syndrome have included behavioral 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, hypotension, tachycardia, nausea, diarrhea), and somatic effects (e.g., muscular rigidity, myoclonus, muscle twitching, hyperreflexia manifested by clonus, and tremor). In the post-marketing period, serotonin syndrome, including potentially life-threatening cases, has been reported in patients treated with antidepressants concomitantly with AZILECT.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid the combination of AZILECT and tricyclic, tetracyclic or triazolopyridine antidepressants, as well as AZILECT and selective serotonin re-uptake inhibitors or serotonin-norepinephrine reuptake inhibitors. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with a tricyclic, tetracyclic, triazolopyridine, SSRI, or SNRI antidepressant. Similarly, at least 14 days should elapse after discontinuing treatment with a tricyclic, tetracyclic, triazolopyridine, SSRI, or SNRI antidepressant before starting AZILECT. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of AZILECT.

Ciprofloxacin and Other CYP1A2 Inhibitors

Rasagiline plasma concentrations may increase up to 2 fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors (see ACTION AND CLINICAL PHARMACOLOGY, *Drug-Drug Interactions* and DOSAGE AND ADMINISTRATION, *Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors*).

Hepatic Impairment

Rasagiline plasma concentration may increase in patients with mild (up to 2 fold, Child-Pugh score 5-6), moderate (up to 7 fold, Child-Pugh score 7-9), and severe hepatic (Child-Pugh score 10-15) impairment. Patients with mild hepatic impairment should be given the dose of 0.5 mg/day. AZILECT should not be used in patients with moderate or severe hepatic impairment. If patients progress from mild to moderate hepatic impairment, AZILECT should be stopped (see ACTION AND CLINICAL PHARMACOLOGY, *Population pharmacokinetics* and DOSAGE AND ADMINISTRATION, *Patients with Hepatic Impairment*).

Renal Impairment

Conclusive data are not available for renally impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment. Due to the absence of adequate safety data, rasagiline should not be administered to patients with moderate to severe renal impairment.

Hypertension and tyramine/rasagiline interaction

Exacerbation of hypertension may occur during treatment with AZILECT. Medication adjustment may be necessary if elevation of blood pressure is sustained. Monitor patients upon initiation or dose increase of AZILECT for new onset hypertension or hypertension that is not adequately controlled.

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, such as Stilton cheese) may contain very high amounts (i.e., > 150 mg) of tyramine and could potentially cause a hypertensive “cheese” reaction in patients taking AZILECT even at the recommended doses due to 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.

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.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using AZILECT for *any* indication. Ideally periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

Dyskinesia Due to Levodopa Treatment

When used as an adjunct to levodopa AZILECT may potentiate dopaminergic side effects and exacerbate pre-existing dyskinesia (treatment-emergent dyskinesia occurred in about 18% of patients treated with 0.5 mg or 1 mg rasagiline as an adjunct to levodopa and 10% of patients who received placebo as an adjunct to levodopa). Decreasing the dose of levodopa may ameliorate this side effect.

Orthostatic Hypotension and Syncope

When used as monotherapy, orthostatic (postural) hypotension was reported in approximately 3% of patients treated with 1 mg rasagiline and 5% of patients treated with placebo. In the monotherapy trial, orthostatic hypotension did not lead to drug discontinuation and premature withdrawal in the rasagiline treated patients or the placebo treated patients.

When used as an adjunct to levodopa, orthostatic hypotension was reported in approximately 6% of patients treated with 0.5 mg rasagiline, 9% of patients treated with 1 mg rasagiline and 3% of patients treated with placebo. Orthostatic hypotension led to drug discontinuation and premature withdrawal from clinical trials in one (0.7%) patient treated with rasagiline 1 mg/day, no patients treated with rasagiline 0.5 mg/day and no placebo-treated patients.

When used as an adjunct therapy to dopamine agonists, orthostatic hypotension was reported in 3.1% of patients treated with 1 mg rasagiline and in 0.6% of patients treated with placebo.

Since dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension, which may lead to syncope, particular caution is advised in patients with a history of orthostatic hypotension, syncope or severe cardiovascular disease.

Clinical trial data suggest that orthostatic hypotension occurs most frequently in the first two months of rasagiline treatment and tends to decrease over time. Some patients treated with AZILECT experienced a mildly increased risk for significant decreases in blood pressure unrelated to standing but while supine.

Hallucinations

In the monotherapy study, hallucinations were reported as an adverse event in 1.3% of patients treated with 1 mg rasagiline and in 0.7% of patients treated with placebo. In the monotherapy trial, hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 1.3% of the 1 mg rasagiline treated patients and in none of the placebo treated patients.

When used as an adjunct to dopamine agonists, hallucinations were reported as an adverse reaction in 1.2% of patients treated with 1 mg/day rasagiline and 1.8% of patients treated with placebo. Hallucinations led to drug discontinuation and premature withdrawal from the clinical trial in 0.6% of patients treated with 1 mg/day rasagiline and in none of the placebo-treated patients.

When used as an adjunct to levodopa, hallucinations were reported as an adverse event in approximately 5% of patients treated with 0.5 mg/day, 4% of patients treated with 1 mg/day rasagiline and 3% of patients treated with placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in about 1% of patients treated with 0.5 mg/day or 1 mg/day and none of the placebo treated patients.

Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with AZILECT or after starting or increasing the dose of AZILECT. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Impulse Control/Compulsive Behaviours

Patients and caregivers should be advised to adhere to dosage instructions given by the physician. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioral symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating have been reported in patients treated with dopamine agonists and/or other dopaminergic treatments for Parkinson's disease, including AZILECT. Safety data from various sources including literature, clinical trials, and post-market analysis have described an addictive pattern of dopamine replacement therapy, in which patients use doses in excess of those required to control their motor symptoms. Because patients may not recognize these behaviors as abnormal, it is important for physicians to specifically ask patients and caregivers to identify new behavior patterns. Review of treatment is recommended if such symptoms develop. These symptoms were generally reversible upon dose reduction or treatment discontinuation (see **ADVERSE REACTIONS**).

Information for Patients

Patients receiving AZILECT should be given the following instructions by the physician:

- Patients should be told that taking more than 1 mg may cause serious side effects which could include a severe headache, seizures, and a sudden rise in blood pressure. Patients should be told to seek immediate emergency medical assistance if they experience these side effects. Patients should contact their doctor or pharmacist immediately if they experience any other unusual symptoms they have not had before or are not mentioned here.
- Patients who are taking ciprofloxacin and other CYP1A2 inhibitors and patients with mild hepatic impairment should use 0.5mg daily of AZILECT.

- The possibility exists that very tyramine-rich foods (e.g., aged cheese such as Stilton) could possibly cause an increase in blood pressure. Patients should be advised to avoid certain foods containing a very large amount of tyramine (e.g., aged cheese) while taking recommended doses of AZILECT because of the potential for large increases in blood pressure. If patients eat food very rich in tyramine and do not feel well after eating, they should contact their healthcare provider.
- Patients should be cautioned of the possibility of developing hallucinations and instructed to report them to their healthcare provider promptly should they develop.
- Patients should be advised to inform their physician if they are taking, or planning to take, any prescription or over-the-counter drugs especially with antidepressants and over-the-counter cold medications since there is a potential for interaction with AZILECT. Patients should not use meperidine with AZILECT.
- Patients taking AZILECT as adjunct to levodopa should be advised there is the possibility of increased dyskinesia and orthostatic (postural) hypotension.
- Patients taking AZILECT as adjunct to dopamine agonists should be advised there is the possibility of increased side effects such as impulse control disorders and sudden sleep onset.
- Patients are advised to monitor for melanomas frequently and on a regular basis because patients with Parkinson's disease have a higher risk of developing melanoma than the general population. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).
- Patients should be instructed to take AZILECT as prescribed. If a dose is missed the next dose should be taken at the usual time on the following day. The patient should not double-up the dose of AZILECT.
- Patients should be told to contact their healthcare provider if they wish to discontinue AZILECT.

Laboratory Tests

No specific laboratory tests are necessary for the management of patients on AZILECT.

Special Populations

Use in Pregnancy

Reproductive studies conducted with rasagiline in animals did not reveal any negative effect at doses much higher than those used in the clinical studies. However, 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.

Nursing Mothers

Experimental data indicated that rasagiline inhibits prolactin secretion and, thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk. Because many drugs are

excreted in human milk, caution should be exercised when AZILECT is administered to a nursing woman.

Use in Children

The safety and effectiveness of AZILECT in patients below 18 years of age have not been established.

Use in the Elderly

Approximately half of patients in clinical trials were 65 years and over. There were no significant differences in the safety profile of the geriatric and non-geriatric patients.

ADVERSE REACTIONS

During the clinical development of AZILECT (rasagiline mesylate tablets), 1523 Parkinson's disease patients received AZILECT as initial monotherapy and as adjunct therapy to dopamine agonists in early stages, or as adjunct therapy to levodopa in more advanced stages of Parkinson's disease. As these populations differ, not only in the adjunct use of dopamine agonists or levodopa during AZILECT treatment, but also in the severity and duration of their disease, they may have differential risks for various adverse events. Therefore, most of the adverse events data in this section are presented separately for each population.

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients Receiving AZILECT as Initial Monotherapy

Adverse events leading to discontinuation in controlled clinical studies:

In the double-blind, placebo-controlled trial (TEMPO) conducted in patients receiving AZILECT as monotherapy, approximately 5% of the 149 patients treated with rasagiline discontinued treatment due to adverse events compared to 2% of the 151 patients who received placebo.

The only adverse event that led to the discontinuation of more than one patient was hallucinations.

Adverse event incidence in a controlled clinical study:

The most commonly observed adverse events that occurred in 5% of patients receiving AZILECT 1 mg as monotherapy (n=149) participating in the double-blind, placebo-controlled trial and that were at least 1.5 times the incidence in the placebo group (n=151), were: flu syndrome, arthralgia, depression, dyspepsia and fall.

Table 1 lists treatment emergent adverse events that occurred in 2% of patients receiving AZILECT as monotherapy participating in the double-blind, placebo-controlled trial and were numerically more frequent than in the placebo group.

Table 1. Treatment Emergent* Adverse Events in AZILECT 1 mg-Treated Monotherapy Patients in TEMPO

Placebo-Controlled Studies Without Levodopa Treatment	AZILECT 1 mg (N=149)	Placebo (N=151)
	% of Patients	% of Patients
Headache	14	12
Arthralgia	7	4
Dyspepsia	7	4
Depression	5	2
Fall	5	3
Flu syndrome	5	1
Conjunctivitis	3	1
Fever	3	1
Gastroenteritis	3	1
Rhinitis	3	1
Arthritis	2	1
Ecchymosis	2	0
Malaise	2	0
Neck Pain	2	0
Paresthesia	2	1
Vertigo	2	1

*Incidence $\geq 2\%$ in AZILECT 1 mg group and numerically more frequent than in placebo group

Other events of potential clinical importance reported by 1% or more of Parkinson’s disease patients receiving AZILECT as monotherapy, and at least as frequent as in the placebo group, in descending order of frequency include: dizziness, diarrhea, chest pain, albuminuria, allergic reaction, alopecia, angina pectoris, anorexia, asthma, hallucinations, impotence, leukopenia, libido decreased, liver function tests abnormal, skin carcinoma, syncope, vesiculobullous rash, vomiting.

There were no significant differences in the safety profile based on age or gender.

Patients Receiving AZILECT as Adjunct to Dopamine Agonists Therapy

Adverse events leading to discontinuation in a controlled clinical study:

In a double-blind, randomized, placebo-controlled trial (ANDANTE) conducted in patients receiving AZILECT as add-on therapy to dopamine agonists, approximately 8% of the 162 patients treated with rasagiline discontinued rasagiline treatment due to adverse reactions compared to 4% of the 164 patients who received placebo.

The adverse reactions that led to the discontinuation of more than one patient were nausea and dizziness.

Adverse Events Incidence in a Controlled Clinical Study

The most commonly observed adverse reactions were those in which the treatment difference for the incidence in AZILECT-treated patients was $\geq 3\%$ greater than the incidence in the placebo-

treated patients and included peripheral edema, fall, arthralgia, cough, and insomnia. Table 2 lists treatment-emergent adverse events that occurred in 2% of patients receiving AZILECT as add-on therapy to dopamine agonists and were numerically more frequent than in the placebo group.

Table 2. Treatment-Emergent* Adverse Events in Patients Receiving AZILECT 1 mg as Adjunct to Dopamine Agonists in ANDANTE

	AZILECT 1 mg (N=162)	Placebo (N=164)
	% of Patients	% of Patients
Dizziness	7	6
Peripheral edema	7	4
Headache	6	4
Nausea	6	4
Fall	6	1
Arthralgia	5	2
Back pain	4	3
Upper Respiratory tract infection	4	2
Cough	4	1
Insomnia	4	1
Fatigue	3	2
Orthostatic hypotension	3	1
Balance disorder	2	1
Constipation	2	0
Abnormal dreams	2	0
Micturition urgency	2	0
Weight increased	2	0

*Incidence 2% in AZILECT 1 mg group and numerically more frequent than in placebo group

Other events of potential clinical importance reported by 1% or more of patients receiving AZILECT as add-on therapy to dopamine agonists, and at least as frequent as in the placebo group, in descending order of frequency include: somnolence, bronchitis, chest pain, cognitive disorder, dyskinesia, flatulence, gastro esophageal reflux disease, hypotension, nervousness, oropharyngeal pain, pain, presyncope, rapid eye movements sleep abnormal, rash, rhinorrhoea, sinusitis, skin papilloma, streptococcal pharyngitis, syncope, viral gastroenteritis, vision blurred.

There were no significant differences in the safety profile based on age or gender.

Patients Receiving AZILECT as Adjunct to Levodopa Therapy

Adverse events leading to discontinuation in controlled clinical studies:

In a double-blind, placebo-controlled trial (PRESTO) conducted in patients treated with AZILECT as adjunct to levodopa therapy, approximately 9% of the 164 patients treated with AZILECT 0.5 mg/day and 7% of the 149 patients treated with AZILECT 1 mg/day discontinued treatment due to adverse events compared to 6% of the 159 patients who received placebo. The

AEs that led to discontinuation of more than one rasagiline treated patient were diarrhea, weight loss, hallucination, and rash. Adverse event reporting was considered more reliable for PRESTO than for the second controlled trial (LARGO); therefore only the adverse event data from PRESTO are presented in this section of labeling.

Adverse event incidence in controlled clinical studies:

The most commonly observed adverse events that occurred in 5% of patients receiving AZILECT 1 mg (n=149) as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (PRESTO) and that were at least 1.5 times the incidence in the placebo group (n=159) in descending order of difference in incidence were dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anorexia, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, ecchymosis, somnolence and paresthesia.

Table 3 lists treatment emergent adverse events that occurred in 2% of patients treated with AZILECT 1 mg/day as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (PRESTO) and that were numerically more frequent than the placebo group. The table also shows the rates for the 0.5 mg group in PRESTO.

Table 3. Incidence of Treatment Emergent* Adverse Events in Patients Receiving AZILECT as Adjunct to Levodopa Therapy in PRESTO

	AZILECT 1 mg + Levodopa (N=149)	AZILECT 0.5 mg + Levodopa (N=164)	Placebo + Levodopa (N=159)
	% of patients	% of patients	% of patients
Dyskinesia	18	18	10
Accidental injury	12	8	5
Nausea	12	10	8
Headache	11	8	10
Fall	11	12	8
Weight loss	9	2	3
Constipation	9	4	5
Postural hypotension	9	6	3
Arthralgia	8	6	4
Vomiting	7	4	1
Dry mouth	6	2	3
Rash	6	3	3
Somnolence	6	4	4
Abdominal pain	5	2	1
Anorexia	5	2	1
Diarrhea	5	7	4
Ecchymosis	5	2	3
Dyspepsia	5	4	4
Paresthesia	5	2	3
Abnormal dreams	4	1	1

Hallucinations	4	5	3
Ataxia	3	6	1
Dyspnea	3	5	2
Infection	3	2	2
Neck pain	3	1	1
Sweating	3	2	1
Tenosynovitis	3	1	0
Dystonia	3	2	1
Gingivitis	2	1	1
Hemorrhage	2	1	1
Hernia	2	1	1
Myasthenia	2	2	1

*Incidence 2% in AZILECT 1 mg group and numerically more frequent than in placebo group.

Several of the more common adverse events seemed dose-related, including weight loss, postural hypotension, and dry mouth.

Other events of potential clinical importance reported in PRESTO by 1% or more of patients treated with rasagiline 1 mg/day as adjunct to levodopa therapy and at least as frequent as in the placebo group, in descending order of frequency include: skin carcinoma, anemia, albuminuria, amnesia, arthritis, bursitis, cerebrovascular accident, confusion, dysphagia, epistaxis, leg cramps, pruritus, skin ulcer.

There were no significant differences in the safety profile based on age or gender.

Other Adverse Events Observed During All Phase II/III/IV Clinical Trials

Rasagiline was administered to approximately 1523 patients during all PD phase II/III/IV clinical trials. About 771 patients received rasagiline for at least one year, approximately 361 patients received rasagiline for at least two years and 245 patients received rasagiline for more than 3 years, with 138 patients treated for more than 5 years. The long-term safety profile was similar to that observed with shorter duration exposure.

The frequencies listed below represent the proportion of the 1523 individuals exposed to rasagiline who experienced events of the type cited.

All events that occurred at least twice (or once for serious or potentially serious events) except those already listed above, trivial events, terms too vague to be meaningful, adverse events with no plausible relation to treatment and events that would be expected in patients of the age studied were reported without regard to determination of a causal relationship to rasagiline.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients, infrequent adverse events are defined as those occurring in less than 1/100 to at least 1/1000 patients and rare adverse events are defined as those occurring in fewer than 1/1000 patients.

Body as a whole: *Frequent:* asthenia. *Infrequent:* chills, face edema, flank pain, photosensitivity reaction

Cardiovascular system: *Frequent:* bundle branch block. *Infrequent:* deep thrombophlebitis, heart failure, migraine, myocardial infarct, phlebitis, ventricular tachycardia. *Rare:* arterial thrombosis, atrial arrhythmia, AV block complete, AV block second degree, bigeminy, cerebral hemorrhage, cerebral ischemia, ventricular fibrillation

Digestive system: *Frequent:* gastrointestinal hemorrhage *Infrequent:* colitis, esophageal ulcer, esophagitis, fecal incontinence, intestinal obstruction, mouth ulceration, stomach ulcer, stomatitis, tongue edema. *Rare:* hematemesis, hemorrhagic gastritis, intestinal perforation, intestinal stenosis, jaundice, large intestine perforation, megacolon, melena

Hemic and Lymphatic system: *Infrequent:* macrocytic anemia. *Rare:* purpura, thrombocytopenia

Metabolic and Nutritional disorders: *Infrequent:* hypocalcemia

Musculoskeletal system: *Infrequent:* bone necrosis, muscle atrophy. *Rare:* arthrosis

Nervous system: *Frequent:* abnormal gait, anxiety, hyperkinesia, hypertonia, neuropathy, tremor *Infrequent:* agitation, aphasia, circumoral paresthesia, convulsion, delusions, dementia, dysarthria, dysautonomia, dysesthesia, emotional lability, facial paralysis, foot drop, hemiplegia, hypesthesia, incoordination, manic reaction, myoclonus, neuritis, neurosis, paranoid reaction, personality disorder, psychosis, wrist drop. *Rare:* apathy, delirium, hostility, manic depressive reaction, myelitis, neuralgia, psychotic depression, stupor

Respiratory system: *Infrequent:* apnea, emphysema, laryngismus, pleural effusion, pneumothorax. *Rare:* interstitial pneumonia, larynx edema, lung fibrosis

Skin and Appendages: *Infrequent:* eczema, urticaria. *Rare:* exfoliative dermatitis, leukoderma

Special senses: *Infrequent:* blepharitis, deafness, diplopia, eye hemorrhage, eye pain, glaucoma, keratitis, ptosis, retinal degeneration, taste perversion, visual field defect. *Rare:* blindness, parosmia, photophobia, retinal detachment, retinal hemorrhage, strabismus, taste loss, vestibular disorder

Urogenital system: *Frequent:* hematuria, urinary incontinence. *Infrequent:* acute kidney failure, dysmenorrhea, dysuria, kidney calculus, nocturia, polyuria, scrotal edema, sexual function abnormal, urinary retention, urination impaired, vaginal hemorrhage, vaginal moniliasis, vaginitis. *Rare:* abnormal ejaculation, amenorrhea, anuria, epididymitis, gynecomastia, hydroureter, leukorrhea, priapism

Postmarketing Experience

The following adverse events have been identified during post-approval use of AZILECT. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Serotonin syndrome characterized by agitation, confusion, rigidity, pyrexia, and myoclonus have been reported by patients treated with antidepressants concomitantly with AZILECT. Cases of impulse control disorder, including pathological gambling, hypersexuality and other impulsive behaviours have been reported.

Cardiovascular system: Cases of elevated blood pressure, including rare cases of hypertensive crisis, associated with ingestion of unknown amounts of tyramine-rich foods; one report of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride.

Renal and urinary disorders: Cases of neurogenic bladder have been reported.

DRUG INTERACTIONS

Meperidine: Serious, sometimes fatal reactions have been precipitated with concomitant use of meperidine (e.g., Demerol and other tradenames) and MAO inhibitors including selective MAO-B inhibitors (see CONTRAINDICATIONS).

Dextromethorphan: The concomitant use of AZILECT and dextromethorphan was not allowed in clinical studies. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Therefore, in view of AZILECT's MAO inhibitory activity, dextromethorphan should not be used concomitantly with AZILECT (see CONTRAINDICATIONS).

Sympathomimetic medications: The concomitant use of AZILECT and sympathomimetic medications was not allowed in clinical studies. Severe hypertensive reactions have followed the administration of sympathomimetics and non-selective MAO inhibitors. Hypertensive crisis has been reported in patients taking the recommended dose of AZILECT and sympathomimetic medication (e.g. ephedrine, phenylephrine). Elevated blood pressure was reported in another patient taking the recommended dose of AZILECT and ophthalmic drops with a sympathomimetic medication (tetrahydrozoline). Because AZILECT is a selective MAOI, hypertensive reactions are not ordinarily expected with the concomitant use of sympathomimetic medications. Nevertheless, caution should be exercised when concomitantly using recommended doses of AZILECT with any sympathomimetic medications including nasal, oral, and ophthalmic decongestants and cold remedies.

MAO inhibitors: AZILECT should not be administered along with other MAO inhibitors, including reversible MAOI (moclobemide) and selective MAO-B inhibitors (selegiline) because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs), Serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants: Concomitant use of SSRI, SNRI, tricyclic, triazolopyridine, and tetracyclic antidepressants with AZILECT should be avoided (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome and Antidepressants).

Levodopa/carbidopa: See ACTION AND CLINICAL PHARMACOLOGY, *Drug-Drug Interactions* and WARNINGS AND PRECAUTIONS, *Dyskinesias Due to Levodopa Treatment*.

Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations may increase up to 2 fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. This could result in increased adverse events. Therefore, patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should use 0.5 mg daily of AZILECT (see ACTION AND CLINICAL PHARMACOLOGY, Drug-Drug Interactions and WARNINGS AND PRECAUTIONS, *Ciprofloxacin and Other CYP1A2 Inhibitors*).

Theophylline: See ACTION AND CLINICAL PHARMACOLOGY, *Drug-Drug Interactions*.

DOSAGE AND ADMINISTRATION

Dosing Considerations:

- The recommended and maximum dose in both monotherapy and adjunct therapy is 1 mg once daily.
- AZILECT can be taken with or without food.

There is no evidence that additional benefit will be obtained from the administration of doses higher than that recommended. Furthermore, higher doses will likely result in a loss of selectivity of rasagiline towards MAO-B with an increase in the inhibition of MAO-A. There is an increased risk of adverse reactions with higher doses as well as an increased risk of hypertensive episode (“cheese reaction”) (see WARNINGS AND PRECAUTIONS, *Tyramine/rasagiline interaction*).

Monotherapy

The recommended AZILECT dose for the treatment of Parkinson’s disease patients is 1 mg administered once daily.

Adjunctive Therapy to Dopamine Agonists

The recommended AZILECT dose as adjunctive therapy to dopamine agonists is 1 mg administered once daily.

Adjunctive Therapy to Levodopa

The dosage of AZILECT shown to be effective in controlled clinical trials for adjunct therapy was 0.5 – 1 mg once daily. The recommended initial dose is 0.5 mg administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Change of levodopa dose in adjunct therapy: When AZILECT is used in combination with

levodopa a reduction of the levodopa dosage may be considered based upon individual response. During the controlled trials of AZILECT as adjunct therapy to levodopa, levodopa dosage was reduced in some patients. In clinical studies, dosage reduction of levodopa was allowed within the first 6 weeks if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In the PRESTO study levodopa dosage reduction occurred in 8% of patients in the placebo group and in 16% and 17% of patients in the 0.5 mg/day and 1 mg/day rasagiline groups, respectively. In those patients who had levodopa dosage reduced, the dose was reduced on average by about 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In the LARGO study levodopa dosage reduction occurred in 6% of patients in the placebo group and in 9% in the rasagiline 1 mg/day group. In patients who had their levodopa dosage reduced, the dose was reduced on average by about 13% and 11% in the placebo and the rasagiline groups, respectively.

Patients with Hepatic Impairment: AZILECT plasma concentration will increase in patients with hepatic impairment. Patients with mild hepatic impairment should use 0.5 mg daily of AZILECT. AZILECT should not be used in patients with moderate to severe hepatic impairment. If patients progress from mild to moderate hepatic impairment, AZILECT should be stopped (see ACTION AND CLINICAL PHARMACOLOGY, *Population pharmacokinetics, Hepatic Impairment* and WARNINGS AND PRECAUTIONS, *Hepatic Impairment*).

Patients with Renal Impairment: Conclusive data are not available for renally impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment. Due to the absence of adequate safety data, rasagiline should not be administered to patients with moderate to severe renal impairment.

Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations are expected to double in patients taking concomitant ciprofloxacin and other CYP1A2 inhibitors. Therefore, patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should use 0.5 mg daily of AZILECT (see ACTION AND CLINICAL PHARMACOLOGY, *Drug-Drug Interaction Ciprofloxacin* and *Effect of other drugs on the metabolism of AZILECT*; and WARNINGS, *Ciprofloxacin and Other CYP1A2 Inhibitors*).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

Symptoms reported following overdose of AZILECT in doses ranging from 3 mg to 100 mg include dysphoria, hypomania, hypertensive crisis, and serotonin syndrome.

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.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

In the post-marketing period, serotonin syndrome has been reported in a patient erroneously treated with a higher than recommended dose of AZILECT (4 mg daily) and tramadol.

Treatment

There is no specific antidote for rasagiline overdose. The following suggestions are offered based upon the assumption that rasagiline overdose may be modeled after non-selective MAO inhibitor poisoning. Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential. For this reason, in cases of overdose with AZILECT, dietary tyramine restriction should be observed for several weeks to avoid the risk of a hypertensive/cheese reaction.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AZILECT (rasagiline mesylate tablets) is a selective irreversible, monoamine oxidase inhibitor indicated for the treatment of idiopathic Parkinson's disease. MAO, a flavin-containing enzyme, is classified into two major molecular species, A and B, and is localized in mitochondrial membranes throughout the body in nerve terminals, brain, liver and intestinal mucosa. MAO regulates the metabolic degradation of catecholamines and serotonin in the CNS and peripheral tissues. MAO-B is the major form in the human brain. 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. Rasagiline at the recommended therapeutic dose was also shown to be a potent and irreversible inhibitor of MAO-B in platelets.

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.

Pharmacodynamics

Platelet MAO activity in clinical studies: Studies in healthy subjects and in Parkinson's disease patients have shown that rasagiline inhibits platelet MAO-B irreversibly. The inhibition lasts at least 1 week after last dose. Almost 25-35% MAO-B inhibition was achieved after a single rasagiline dose of 1 mg/day and more than 55% of MAO-B inhibition was achieved after a single rasagiline dose of 2 mg/day. Over 90% inhibition was achieved 3 days after rasagiline daily dosing at 2 mg/day and this inhibition level was maintained 3 days post-dose. Multiple doses of rasagiline of 0.5, 1 and 2 mg per day resulted in complete MAO-B inhibition.

Tyramine sensitivity and selectivity for MAO-B: Results of a special tyramine challenge study indicate that rasagiline is selective for MAO-B at recommended doses (0.5 to 1.0 mg daily) and can ordinarily be used without dietary tyramine restriction. The results of a clinical trial designed to examine the effects of AZILECT on blood pressure when it is administered with increasing doses of tyramine indicates the functional selectivity can be incomplete when healthy subjects ingest large amounts of tyramine while receiving recommended doses of AZILECT. The selectivity for inhibiting MAO-B diminishes in a dose-related manner.

Pharmacokinetics

Rasagiline in the range of 1- 6 mg demonstrated a more than proportional increase in AUC, while C_{max} was dose proportional. Its mean steady-state half life is 3 hours but there is no correlation of pharmacokinetics with its pharmacological effect because of its irreversible inhibition of MAO-B.

Absorption: Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%.

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, AZILECT can be administered with or without food (see DOSAGE AND ADMINISTRATION).

Distribution: The mean volume of distribution at steady-state is 87 L indicating that the tissue binding of rasagiline is in excess of plasma protein binding. 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 and Elimination: 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 (AI), 3-hydroxy-N-propargyl-1-aminoindan (3-OH-PAI) and 3-hydroxy-1-aminoindan (3-OH-AI). *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on cytochrome P450 (CYP) system, with CYP 1A2 being the major iso-enzyme involved in rasagiline metabolism. Glucuronide conjugation of rasagiline and its metabolites, with subsequent urinary excretion, is the major elimination pathway.

After oral administration of ¹⁴C-labeled rasagiline, elimination occurred primarily via urine and secondarily via feces (62% of total dose in urine and 7% of total dose in feces over 7 days), with a total recovery of 84% of the dose over a period of 38 days. Less than 1% of rasagiline was excreted as unchanged drug in urine.

Population pharmacokinetics

Hepatic Impairment: Following repeat dose administration (7 days) of rasagiline (1 mg/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 WARNINGS AND PRECAUTIONS, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION, *Patients with Hepatic Impairment*).

Renal Impairment: Conclusive data are not available for renally impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment. Due to the absence of adequate safety data, rasagiline should not be administered to patients with moderate to severe renal impairment.

Geriatric: Since age has little influence on rasagiline pharmacokinetics, it can be administered at the recommended dose in the elderly.

Pediatric: AZILECT has not been investigated in patients below 18 years of age.

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

Drug-Drug Interactions:

Tyramine Effect (see WARNINGS AND PRECAUTIONS, *Tyramine/rasagiline Interaction, Information for Patients* and OVERDOSAGE).

Levodopa: Data from population pharmacokinetic studies comparing rasagiline clearance in the presence and absence of levodopa have given conflicting results. Although there may be some increase in rasagiline blood levels in the presence of levodopa, the effect is modest and rasagiline dosing need not be modified in the presence of levodopa.

Effect of other drugs on the metabolism of AZILECT: *In vitro* metabolism studies showed that CYP 1A2 was the major enzyme responsible for the metabolism of rasagiline. There is the potential for inhibitors of this enzyme to alter AZILECT clearance when co-administered (see WARNINGS AND PRECAUTIONS, *Ciprofloxacin and Other CYP1A2 Inhibitors* and DOSAGE AND ADMINISTRATION, *Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors*).

Ciprofloxacin: When ciprofloxacin, an inhibitor of CYP 1A2, was administered to healthy volunteers (n=12) at 500 mg (BID) with 2 mg/day rasagiline, the AUC of rasagiline increased by 83% and there was no change in the elimination half life (see WARNINGS AND

PRECAUTIONS, *Ciprofloxacin and Other CYP1A2 Inhibitors* and DOSAGE AND ADMINISTRATION, *Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors*).

Theophylline: Co-administration of rasagiline 1 mg/day and theophylline, a substrate of CYP 1A2, up to 500 mg twice daily to healthy subjects (n=24), did not affect the pharmacokinetics of either drug.

Antidepressants: Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combination of tricyclic, tetracyclic or triazolopyridine antidepressants, selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selective MAO-B inhibitors (see WARNINGS AND PRECAUTIONS).

Effect of AZILECT on other drugs: No additional *in vivo* trials have investigated the effect of AZILECT on other drugs metabolized by the cytochrome P450 enzyme system. *In vitro*, studies showed that rasagiline at a concentration of 1µg/ml (equivalent to a level that is 160 times the average C_{max} ~ 5.9-8.5 ng/mL in Parkinson's disease patients after 1 mg rasagiline multiple dosing, did not inhibit cytochrome P450 isoenzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline is unlikely to cause any clinically significant interference with substrates of these enzymes.

STORAGE AND STABILITY

Storage: Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F)

DOSAGE FORMS, COMPOSITION AND PACKAGING

AZILECT (rasagiline mesylate tablets) 0.5 mg are white to off-white, round, flat, beveled tablets, debossed with "GIL" and "0.5" below on one side and plain on the other.

AZILECT (rasagiline mesylate tablets) 1 mg are white to off-white, round, flat, beveled tablets, debossed with "GIL" and "1" below on one side and plain on the other.

Each AZILECT tablet also contains the following inactive ingredients: colloidal silicon dioxide, mannitol, starch, pregelatinized starch, stearic acid and talc.

They are supplied as follows:

Bottles of 30 tablets

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

Description: Rasagiline mesylate is a propargyl amine-based drug indicated for the treatment of idiopathic Parkinson's disease.

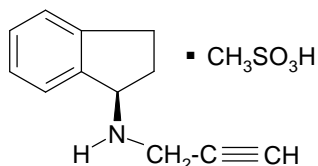
Common Name: Rasagiline mesylate

Chemical Name: N-Propargyl-1(R)-aminoindan mesylate

Chemical Abstract

Service (CAS) Name: 1H-Inden-1-amine, 2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate

Structural Formula: $(C_{12}H_{13}N).CH_4SO_3$



Molecular Weight: 267.34

Physical Form: White to off-white powder

Solubility: Freely soluble in water or ethanol and sparingly soluble in isopropanol

CLINICAL TRIALS

In phase II/III premarketing trials approximately 1361 patients received AZILECT with 771 being treated for at least one year, approximately 361 patients treated for at least two years, and 245 receiving AZILECT for more than 3 years. In a phase IV clinical trial, 162 patients received AZILECT for a duration of 18 weeks.

The effectiveness of AZILECT for the treatment of Parkinson's disease was established in four 18- to 26-week, randomized, placebo-controlled trials. In one of these trials study TVP-1012/232 (TEMPO) AZILECT was given as initial monotherapy treatment, in one as adjunctive therapy to dopamine agonists TVP-1012/103 (ANDANTE) and in the other two studies as adjunctive therapy to levodopa TVP-1012/133 (PRESTO) and TVP-1012/122 (LARGO).

Monotherapy Use of AZILECT

The monotherapy trial (TEMPO) was a double-blind, randomized, fixed-dose parallel group 26-week study in early Parkinson's disease patients not yet receiving any concomitant dopaminergic therapy at the start of the study. The majority of the patients were not treated with any anti-

Parkinson’s disease medication before receiving AZILECT treatment.

The first phase was placebo-controlled in which 404 patients were randomly assigned to receive placebo (138 patients), rasagiline 1 mg/day (134 patients) or rasagiline 2 mg/day (132 patients). Patients were not allowed to take levodopa, dopamine agonists, selegiline or amantadine, but if necessary, could take stable doses of anticholinergic medication. The average Parkinson’s disease duration was approximately 1 year (range 0 to 11 years). Patients completing the first 26 weeks or patients requiring additional anti-PD therapy could start the second phase of double-blind treatment in which all patients received rasagiline, 1 or 2 mg once daily.

Three hundred eighty patients entered the second phase. Patients who received rasagiline in the first phase remained on their originally assigned dose. Patients who received placebo in the first phase were switched to rasagiline, 2 mg once daily.

The primary measure of effectiveness was the change from baseline in the total score of the Unified Parkinson’s Disease Rating Scale (UPDRS), [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.

Rasagiline (1 or 2 mg once daily) had a significant beneficial effect relative to placebo on the primary measure of effectiveness in patients receiving six months of treatment and not on dopaminergic therapy. Patients who received rasagiline had significantly less worsening in the UPDRS score, compared to those who received placebo. The effectiveness of rasagiline 1 mg and 2 mg was comparable. Table 4 displays the results of the monotherapy trial.

Table 4. Early Parkinson’s Disease Patients not on Dopaminergic Therapy (TEMPO)

Primary Measure of Effectiveness: Change in total UPDRS score			
	Baseline score	Change from baseline to termination score	p-value vs. placebo
Placebo	24.5	3.9	---
1.0 mg/day	24.7	0.1	0.0001
2.0 mg/day	25.9	0.7	0.0001

For the comparison between rasagiline 1mg/day and placebo, no differences in effectiveness based on age or gender were detected.

In addition in the TEMPO study the secondary measurements of effectiveness, UPDRS ADL (Activities of Daily Living) subscale score and Motor function subscale score, showed improvements consistent with the primary endpoint.

Adjunctive Use of AZILECT With Dopamine Agonists

The trial that investigated rasagiline as add-on therapy to dopamine agonists was a double-blind, randomized, fixed-dose, parallel group, 18-week study (ANDANTE). Early Parkinson's disease patients were on stable dopamine agonist therapy for 30 days and were either unable to receive an optimal therapeutic dose of dopamine agonist due to intolerable side effects or required an additional therapeutic agent because their optimal dose of dopamine agonist was no longer sufficient to control Parkinson's disease symptoms. Patients experiencing moderate to severe motor fluctuations and patients with an impulse control disorder were excluded from the study.

In this trial, 164 patients received placebo and 162 patients were treated with rasagiline 1 mg/day. The average Parkinson's disease duration was approximately 2 years (range 0.1 to 14.5 years).

The primary measure of effectiveness was the change from baseline to week 18 in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS), [mentation (Part I) + activities of daily living (ADL) (Part II) + motor function (Part III)].

Rasagiline 1 mg had a significant beneficial effect relative to placebo on the primary measure of effectiveness in patients receiving stable dopamine agonist therapy. Table 5 displays the results of the add-on to dopamine agonist trial.

Table 5. Early Parkinson's Disease Patients Receiving AZILECT as Adjunct Therapy with Stable Dopamine Agonist Therapy (ANDANTE)

Primary Measure of Effectiveness: Change in total UPDRS score			
	Baseline score	Change from baseline to termination score	p-value vs. placebo
Placebo	29.8	-1.2	---
Rasagiline 1.0 mg/day	32.1	-3.6	0.012

Adjunctive Use of AZILECT With Levodopa

Two multicenter, randomized, multinational trials were conducted in more advanced Parkinson's disease patients treated chronically with levodopa and experiencing motor fluctuations (including but not limited to, end of dose "wearing off," sudden or random "off," etc) Studies TVP-1012/133 (PRESTO) and TVP-1012/122 (LARGO). The first (PRESTO) was conducted in North America (U.S. and Canada) and compared two doses (0.5 mg and 1 mg daily) of rasagiline and placebo while the second (LARGO) was conducted outside of North America (several European countries, Argentina, Israel) and studied a single dose (1 mg daily) of rasagiline, a COMT inhibitor with each levodopa dose and placebo. Patients had had Parkinson's disease for an average of 9 years (range 5 months to 33 years), 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 kept home diaries just prior to baseline and at specified intervals during the trial. Diaries recorded one of the following four conditions for each half-hour interval over a 24-hour period: "ON" (period of relatively good

function and mobility) as either “ON” with no dyskinesia or without troublesome dyskinesia, “ON” with troublesome dyskinesia, “OFF” (period of relatively poor function and mobility) or asleep. “Troublesome” dyskinesia is defined as that which interferes with the patient’s daily activity. All patients had been inadequately controlled and were experiencing motor fluctuations typical of advanced stage disease despite receiving levodopa/decarboxylase inhibitor. The average dose of levodopa/decarboxylase inhibitor was approximately 700 to 800 mg (range 150 to 3000 mg/day). 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 (PRESTO) approximately 35% were on entacapone. The majority of patients taking entacapone were taking a dopamine agonist as well.

In both trials the primary measure of effectiveness was the change in the mean number of hours that were spent in the “OFF” state at baseline compared to the mean number of hours that were spent in the “OFF” state during the treatment period. Secondary measures of effectiveness included global assessments of improvement by the examiner, ADL subscale scores when OFF and UPDRS motor while ON. A reduction in the UPDRS score represents improvement and a beneficial change from baseline appears as a negative number.

PRESTO was a double-blind, randomized, fixed-dose parallel group trial conducted in 472 levodopa-treated Parkinson’s disease patients who were experiencing motor fluctuations. 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.

LARGO was a double-blind, randomized, parallel group trial conducted in 687 levodopa-treated Parkinson’s disease patients who were experiencing motor fluctuations. Patients were randomly assigned to receive placebo (229 patients), rasagiline 1 mg/day (231 patients) or an active comparator, a COMT inhibitor taken along with scheduled doses of levodopa/decarboxylase inhibitor (227 patients). Patients were treated for 18 weeks. Patients averaged approximately 5.6 hours daily in the “OFF” state at baseline as confirmed by home diaries.

In both studies rasagiline 1 mg once daily reduced “OFF” time compared to placebo when added to levodopa in patients experiencing motor fluctuations (Tables 6 and 7). The lower dose (0.5 mg) of rasagiline also significantly reduced “OFF” time (Table 6), but had a numerically smaller effect than the 1mg dose of rasagiline.

Table 6. Advanced* Parkinson’s Disease Patients Receiving AZILECT as Adjunct Therapy with Levodopa (PRESTO)

Primary Measure of Effectiveness: Change in mean total daily “OFF” time			
	Baseline (hours)	Change from baseline to treatment period (hours)	p-value vs. placebo
Placebo	6.0	-0.9	---
0.5 mg/day	6.0	-1.4	0.0199
1.0 mg/day	6.3	-1.9	< 0.0001

* All recruited patients were experiencing motor fluctuations typical of advanced stage disease.

Table 7. Advanced* Parkinson’s Disease Patients Receiving AZILECT as Adjunct Therapy with Levodopa (LARGO)

Primary Measure of Effectiveness: Change in mean total daily “OFF” time			
	Baseline (hours)	Change from baseline to treatment period (hours)	p-value vs. placebo
Placebo	5.5	- 0.40	---
1.0 mg/day	5.6	-1.2	0.0001
COMT inhibitor with each levodopa dose	5.6	-1.2	<0.0001

* All recruited patients were experiencing motor fluctuations typical of advanced stage disease.

In both studies, dosage reduction of levodopa was allowed within the first 6 weeks if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In PRESTO, levodopa dosage reduction occurred in 8% of patients in the placebo group and in 16% and 17% of patients in the 0.5 mg/day and 1 mg/day rasagiline groups, respectively. In those patients who had levodopa dosage reduced, the dose was reduced on average by about 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In LARGO, levodopa dosage reduction occurred in 6% of patients in the placebo group and in 9% in the rasagiline 1 mg/day group. In patients who had their levodopa dosage reduced, the dose was reduced on average by about 13% and 11% in the placebo and the rasagiline groups, respectively.

For the comparison between rasagiline 1 mg/day and placebo in both studies, no differences in effectiveness based on age or gender were detected.

Several secondary outcome assessments in the two studies showed statistically significant improvements with rasagiline. These included effects on the activities of daily living (ADL)

subscale of the UPDRS performed during an “OFF” period, and the motor subscale of the UPDRS as performed during an “ON” period.

DETAILED PHARMACOLOGY

Rasagiline has been developed as the single (R)-isomer, which is three orders of magnitude more potent than the (S)-isomer, as a non-reversible inhibitor of MAO-B. It has been shown that there is no bioconversion of the isomers under *in vivo* exposure conditions in human plasma or during storage.

The primary pharmacodynamic action of rasagiline is selective inhibition of monoamine oxidase type B (MAO-B). MAO-B inhibition elicits additional primary pharmacodynamic effects due to elevation of brain monoamine levels and dopamine in particular. These include protection against MPTP-induced neurotoxicity and possible amelioration in the performance of motor tasks and of cognition that had been impaired by neural injury. Apart from MAO inhibitory activity, rasagiline exhibited notable neuroprotective potency in *in vitro* and *in vivo* neurodegeneration models. This neuroprotective activity exhibited by rasagiline is considered as a secondary pharmacodynamic effect. Collectively, these pharmacological effects of rasagiline are suggested to underlie its beneficial activity in PD patients.

Rasagiline is a potent, irreversible, selective MAO-B inhibitor that effectively crosses the blood-brain barrier after oral administration and retains its MAO-B inhibitory activity after repeated dosing with IC_{50} values for human and rat brain of 2.5-20 nM. *In vivo* selective inhibition of brain MAO-B was confirmed in rats, mice, dogs and common marmosets. The daily oral dose (0.05 mg/kg/day) required to inhibit rat brain MAO-B activity by more than 90% is $1/10^{\text{th}}$ of the dose of selegiline required to elicit the same effect. The higher MAO-B inhibitory potency of rasagiline as compared with selegiline was also demonstrated in the mouse MPTP-induced neurotoxicity model. Rasagiline selectivity for MAO-B inhibition upon repeated treatment is reflected in the high ED_{50} ratios (MAO-A)/(MAO-B) of 45 and 77 for rat brain and liver, respectively.

In vivo microdialysis in rats confirmed that extracellular striatal dopamine is elevated, but without concomitant decreases in dopamine metabolites, after repeated oral administration of doses of rasagiline selective for MAO-B inhibition. Restoration of normal motor activity, after acute administration of rasagiline, was demonstrated in animal models of haloperidol or -MPT-induced dopaminergic dysfunction. Chronically administered rasagiline (1-4 months) exhibits beneficial effects in models of hypoxia-induced motor dysfunction and cognitive deficits. Selegiline, by comparison whilst showing activity in some motor dysfunction models, had no activity in models of cognitive impairment.

The beneficial effects of chronically administered rasagiline may involve, in addition to MAO-B inhibition, a neuroprotective action. Rasagiline increased the survival of primary neurons and neuron-like cell lines. The *in vitro* neuroprotective activity of rasagiline was confirmed using several *in vivo* models of neuronal insult. The S-enantiomer of rasagiline, while inactive against MAO-B, exhibited an almost equivalent neuroprotective effect. Thus, it is suggested that the neuroprotective properties of rasagiline are not mediated by MAO inhibition. Selegiline has a

lesser effect in the same systems and moreover, unlike rasagiline, produces a neurotoxic metabolite (L-metamphetamine).

It has been shown that rasagiline has no effect on the cardiovascular system in the dog and rat at doses that are at least 10-fold higher than the clinical dose of 1 mg/day in patients. An Irwin screen in rats did not reveal any potential for unwanted pharmacological actions on the central nervous system. No respiratory adverse events were detected in any of the dog telemetry study, in repeated dose toxicology studies and in clinical studies (Phases I, II and III).

As rasagiline may also be used as adjunctive therapy with levodopa, the effect of rasagiline on the levodopa pressor response was evaluated. It was shown that rasagiline did not potentiate the hypotensive effect of levodopa/carbidopa, when the compounds were co-administered repeatedly. There was no manifestation of the tyramine pressor response in rats given rasagiline at doses of up to 0.5 mg/kg/day (p.o.) for 21 days.

Pharmacokinetics

Absolute bioavailability, derived from comparison of AUC values for oral and intravenous dosing, can be estimated as 53-69% in rats and 13-22% in dogs.

In rats and dogs, intravenously administered rasagiline is rapidly cleared at rates that exceed plasma flow through the liver and kidneys indicating extra-hepatic and extra-renal clearance. The volume of distribution exceeds that of the total body water indicating preferential localisation in tissues other than blood.

Oral studies with ¹⁴C-rasagiline confirmed the rapid clearance of unchanged drug from the systemic circulation and the longer persistence of derived components. In rats given a single oral dose (0.37 mg/kg) of ¹⁴C-rasagiline mesylate less than 20% of the dose remained in the gastrointestinal tract at 0.25 and 0.5 hours, plasma radioactivity was maximal at 0.25 hours declining thereafter with a terminal half-life of 61 hours. Plasma concentrations of unchanged drug declined with a terminal half-life of *ca.* 1 hour indicating an extensive first pass metabolism effect. In mice unchanged drug respectively accounted for 12 and 22% of the plasma radioactivity after oral doses of ¹⁴C-rasagiline at 1 and 45 mg/kg. In rats the amount of unchanged drug at 0.25 hours after an oral dose (0.37 mg/kg) of ¹⁴C-rasagiline accounted for *ca.* 10% of the plasma radioactivity. In the dog unchanged drug respectively accounts for 4.8% and 1.3% of the administered radioactivity at 1 and 2 hours after an oral dose of ¹⁴C-rasagiline at 1 mg/kg.

The tissue distribution of ¹⁴C-rasagiline (0.37 mg/kg) was studied in albino and pigmented rats. Tissue radioactivity peaked between 0.25 and 0.5 hours, except for large intestine, urinary bladder and Lacrimal glands (about 4 hours). The tissue: whole blood ratios exceeded unity, and uptake was highest in liver. The high tissue:whole blood ratios were consistent with the high volume of distribution. Uptake was higher and persisted for longer in the eyes and skin of pigmented rats and there was autoradiographic evidence of persistence of radioactivity in the arterial walls at 24 hours. *In vitro* plasma protein binding varied between 70.7% and 75.2% for mice, 75.2% to 81.3% for rats and 80.9% and 88.9% for dogs. On the other hand, *ex vivo* binding to plasma proteins in dogs amounted to 17% at 1 and 2 hours, 28% at 4 hours and 44% at 8 hours

after a single oral dose of ^{14}C -rasagiline.

The biotransformation of rasagiline was investigated using microsomal preparations from mice, rats, dogs and humans and plasma and urinary metabolites were profiled after *in vivo* dosing of mice, rats and dogs. Profiling of faecal metabolites was not undertaken because of the predominance of the urinary route of excretion in all species. Qualitatively similar metabolic profiles were established for mice, rats, dogs and humans. It is proposed that the parent molecule (PAI) undergoes *N*-dealkylation to form AI (aminoindan) and hydroxylation to form 3-hydroxy-*N*-propargyl-1-aminoindan (3-OH-PAI). There is also minor oxidative deamination to indanone. AI and 3-OH-PAI undergo further hydroxylation and/or *N*-dealkylation to form 3-OH-AI, 3-keto-PAI and 3-keto-AI and indanone undergoes further reduction to indanol. There is also conjugation of PAI and its metabolites with sulphate and/or glucuronic acid as well as *N*-acetylation. The metabolism of PAI appears to be CYP 450 dependent. The data generated permit qualitative comparison of the metabolite profile in plasma and semi-quantitative comparisons of the urinary metabolite profiles in mice, rats, dogs and humans. The semi-quantitative comparison of urinary metabolites is tabulated below:

Table 8. Semi-Quantitative Comparison of Urine Metabolites in Different Species (% of administered dose in urine collected 0 – 48 hours post dose)

Species	Mice	Rat	Dog	Human
Study Number	SB-2001-039	SB-2001-001	SB-2002-007 ³	SB-2001-018 ¹
Metabolite				
Polar	6.2 - 32	37 - 43	69	21
3- OH-AI	4.7 – 7.0	14 – 16	2.8	2.0
3-keto-AI	0.9 -1.7	1.8 – 3.2	1.1	
AI	7.7 – 18.5	7.5 – 11.1	2.5	21
3-OH-PAI	< 1	< 1	<1	
3-keto PAI		< 1		
PAI	1.7 - 3.5	1.0 – 3.4	<1	0.7 – 1.4
Indanone		<1	Traces	
Phase II metabolites in different species				
Conjugated PAI ²	1.2 – 3.3 ³	0.4 – 1.0	<0.6	5.5 ⁴
Conjugated AI ²		0.7 – 1.1	0.6	7 ⁴
Conjugated 3-OH-PAI ²	2 – 3.5 ³	.3 – 2.1	8.0	14 ⁴
3-OH- AAI		7.9 – 9.2		1.9 – 2.3 ⁴
3-keto-AAI		0.7 – 1.4		<2 ⁴

1 Pooled urine samples from 6 healthy volunteers, that were treated with a single oral dose of 2 mg ^{14}C -rasagiline mesylate (free base equivalent).

2 Enzymatic hydrolysis of conjugated metabolites was performed in a buffer containing β -glucuronidase/ sulfatase type H-5 from *H. pomatia*. The specificity of the hydrolysis was further investigated by addition of saccharolactone, an inhibitor of β -glucuronidase, but not sulfatase. This reaction was carried out in order to identify phase-1 metabolites that were conjugated with glucuronic acid/ sulfate (phase II).

3 Metabolites in urine collected 0 – 24 h post dose

4 Metabolites in urine collected 0 – 4 h post dose

Mass balance studies were conducted in mice, rats and dogs following oral administration of rasagiline. In mice there was 79.4% recovery of the administered radioactivity in excreta (73.6% urine and 5.8% faeces) within 96 hours of a single oral dose (1 mg/kg) of ¹⁴C-rasagiline. In rats the amount of radioactivity excreted via the urine within 168 hours of a single oral dose (0.37 mg/kg) of ¹⁴C-rasagiline amounted to 89.4% of the administered dose with 5.8% of the dose recovered from faeces during the same time interval. The total recovery of radioactivity from excreta within 168 hours was therefore 95.2%. Dogs excreted approximately 83% of the administered radioactivity via urine within 144 hours of a single oral dose (1 mg/kg) of ¹⁴C-rasagiline. Excretion in faeces amounted to 5.3% whilst 4.8% was recovered from cage washings over the same time period. Thus the total recovery of radioactivity within 144 hours amounted to 93%.

Systemic (plasma) exposure to PAI and AI was quantified during the course of the majority of the toxicology studies. These investigations showed that exposure was linear at doses higher than the pharmacological selectivity for inhibition of MAO-B and was maintained up to about 5 mg/kg/day. At the higher doses that were used to satisfy regulatory requirements for the design of toxicological investigations exposure to PAI and AI was characterized by non-linear kinetics. Although this possibly indicated saturation of the elimination processes for both PAI and AI accumulation was only evident at the highest dose (60 mg/kg/day) used for mice in the 13-week study and the highest dose (21 mg/kg/day) used for the 52-week oral toxicity study in dogs. Surprisingly, and despite the rapid elimination half-life for PAI, repeated dosing sometimes resulted in greater exposure than seen after single doses. This is consistent with the irreversible binding of rasagiline to its target enzyme thus rendering enzyme turnover time an important determinant of kinetic behavior. This possibility is further substantiated by the reliance upon extra-hepatic and extra-renal clearance and the high volume of distribution already discussed. It is also likely that the binding to abundant intestinal MAO sites contributes to the high first pass effect. Thus it is conceivable that rasagiline specifically binds to specific tissue sites (probably MAO) until the available binding sites are saturated. Once the saturation threshold has been reached then the excess unbound drug will appear in plasma.

TOXICOLOGY

Acute Toxicity Studies

At the outset of the program the hydrochloride salt was selected as the development candidate. Subsequently the mesylate salt (designated TVP-1012) was chosen because of its superior stability profile. Bridging studies confirmed the similarity of the pharmacokinetic and toxicological profiles of the two salts. There was therefore no necessity to repeat the toxicology studies with the hydrochloride salt that were completed prior to the switch.

Single dose toxicity studies were conducted by the intravenous route in rats and by the oral route in mice, rats and dogs. Studies were initially conducted with the hydrochloride salt and subsequently with the more stable mesylate salt. Mortalities were induced in rats by intravenous doses ≥ 69 mg/kg/day. Mortalities were induced in mice at oral doses of ≥ 206 mg/kg, in rats at oral doses ≥ 155 mg/kg and in dogs at oral doses of ≥ 84 mg/kg. Death was a result of the

functional neuropharmacological changes that can be anticipated when excessive doses of a molecule capable of inhibiting the oxidation of biogenic amines is administered. The maximal non-lethal oral dose for rats and mice was about 100 mg/kg/day and the maximum tolerable dose (MTD) in dogs was 42 mg/kg. These doses represent considerable multiples of the recommended clinically relevant maximum dose of 1 mg/patient/day.

Long-Term Toxicity Studies

The rat and dog were selected for the conduct of repeat dose toxicity studies, both species having been shown to be pharmacologically responsive to rasagiline-induced inhibition of MAO-B. Repeat dose intravenous toxicity studies of 4-weeks duration were conducted at maximum doses of 3 mg/kg/day in rats and 5 mg/kg/day in dogs. Repeat dose oral toxicity studies of up to 26 weeks duration were conducted in rats employing doses spanning the range 0.14 to 17 mg/kg/day and of up to 52 weeks duration in dogs employing doses spanning 0.28 to 21.0 mg/kg/day. The multiples of the systemic exposures to PAI and AI across the range of doses used for the repeat dose toxicity studies in rats and dogs are compared with the clinically relevant human exposure at the maximum recommended daily dose of 1 mg/day/patient in the following Table.

Table 9. Comparison of the Achieved Systemic Exposures to PAI and AI Over the Range of Doses used for Repeat Dose Oral Toxicity Studies in Rats and Dogs with Human Clinical Exposure at 1 mg/Patient/Day.

Species	Sex	Dose	No. of Daily Doses	C _{max} (ng/ml)		AUC _t (ng•h/ml)	
				PAI	AI	PAI	AI
Rat	Male	0.7 mg/kg/day	90	64	17	74	50
		17.0 mg/kg/day	28	1530	679	2706	3399
	Female	0.7 mg/kg/day	90	80	31	78	89
		17.0 mg/kg/day	28	1537	827	2829	6528
Dog	Male	0.7 mg/kg/day	85	74	25	65	95
		21.0 mg/kg/day	28	1604	1388	2807	7280
	Female	0.7 mg/kg/day	85	16	20	29	69
		21.0 mg/kg/day	28	5358	1745	5781	10785
Human*	Male	1 mg/patient	10 weeks	5.8	2.0	9.6	6.6
	Female	1 mg/patient		6.1	3.2	10.8	10.4

* Human exposure data taken from clinical study TVP-1012/231: Tolerability of TVP-1012, a Novel MAO-B Inhibitor, in Parkinson's disease patients.

Thus the lowest doses used for the repeat dose toxicity studies afforded at least a 2-fold multiple of the mean C_{max} and AUC_{last} values for PAI in humans receiving 1 mg/day. By contrast, the highest doses used for the repeat dose toxicology studies afforded at least a 250-fold multiple of C_{max} and AUC_{last} values for PAI in humans receiving 1 mg/day.

After intravenous and oral dosing the principal manifestations of toxicity were related to the loss of selectivity for MAO-B (i.e. reduced food intake and weight gain and hyperactivity and/or aggression in rats). At the higher oral doses these findings were sometimes accompanied by increases in liver weight and adaptive changes in hepatocyte morphology in rats. The liver

changes were consistent with changes observed in rats treated with hepatic microsomal enzyme inducers, there was however no evidence from studies that measured hepatic microsomal proteins to support this hypothesis. Suspected changes in thyroid and bladder morphology identified in the rat 13-week oral study were not corroborated by findings in either the 4-week or 26-week rat oral studies. The no adverse effect levels (NOAELs) defined after 26 weeks' treatment of rats and 52 weeks' treatment of dogs were 5.1 mg/kg/day (for both rats and dogs). In terms of AUC_{last} values, the animal NOAELs afford multiples of at least 15-fold with respect to exposure to PAI at the clinical dose of 1 mg/patient/day.

Studies were also conducted to examine whether co-administration of rasagiline with levodopa and a peripheral decarboxylase inhibitor (carbidopa) can produce effects other than the expected dopaminergic actions. There were no effects in rats or dogs given rasagiline/carbidopa/levodopa that could not be attributed to amplification of the effects of levodopa/carbidopa.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two year carcinogenicity studies were conducted in CD-1 mice at oral (gavage) doses of 1, 15, and 45 mg/kg and in Sprague-Dawley rats at oral (gavage) doses of 0.3, 1, and 3 mg/kg (males) or 0.5, 2, 5, and 17 mg/kg (females). In rats, there was no increase in tumors at any dose tested. Plasma exposures at the highest dose tested were approximately 33 and 260 times, in male and female rats, respectively, the expected plasma exposures in humans at the maximum recommended dose (MRD) of 1 mg/day.

In mice, there was an increase in lung tumors (combined adenomas/carcinomas) at 15 and 45 mg/kg males and females. Plasma exposures associated with the no-effect dose (1 mg/kg) were approximately 5 times those expected in humans at the MRD.

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

Mutagenesis: Rasagiline was reproducibly clastogenic in *in vitro* chromosomal aberration assays in human lymphocytes in the presence of metabolic activation and was mutagenic and clastogenic in the *in vitro* mouse lymphoma TK assay in the absence and presence of metabolic activation. Rasagiline was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vivo* unscheduled DNA synthesis assay, and the *in vivo* micronucleus assay in CD-1 mice. Rasagiline was also negative in the *in vivo* micronucleus assay in CD-1 mice when administered in combination with levodopa/carbidopa.

Impairment of Fertility: Rasagiline had no effect on mating performance or fertility in male rats treated prior to and throughout the mating period, or in female rats treated from prior to mating through day 17 of gestation at oral doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [1 mg/day]). The effect of rasagiline administered in combination with levodopa/carbidopa on mating and fertility has not been examined.

Reproductive Toxicity Studies

No effect on embryo-fetal development was observed in a combined mating/fertility and

embryo-fetal development study in female rats at doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [MRHD, 1 mg/day]).

In pregnant rabbits administered rasagiline throughout the period of organogenesis at oral doses of up to 36 mg/kg/day, no developmental toxicity was observed. At the highest dose tested, the plasma AUC was approximately 800 times that in humans at the MRHD.

In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) orally, from the beginning of organogenesis to day 20 post-partum, offspring survival was decreased and offspring body weight was reduced at doses of 0.3 mg/kg/day and 1 mg/kg/day (10 and 16 times the expected plasma rasagiline exposure [AUC] at the MRHD). No plasma data were available at the no-effect dose (0.1 mg/kg); however, that dose is 1 times the MRHD on a mg/m² basis. Rasagiline's effect on physical and behavioral development was not adequately assessed in this study.

Rasagiline may be given as an adjunct therapy to levodopa/carbidopa treatment. In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day) (alone and in combination) throughout the period of organogenesis, there was an increased incidence of wavy ribs in fetuses from rats treated with rasagiline in combination with levodopa/carbidopa at 1/80/20 mg/kg/day (approximately 8 times the plasma AUC expected in humans at the MRHD and 1/1 times the MRHD of levodopa/carbidopa [800/200 mg/day] on a mg/m² basis). In a study in which pregnant rabbits were dosed throughout the period of organogenesis with rasagiline alone (3 mg/kg) or in combination with levodopa/carbidopa (rasagiline: 0.1, 0.6, 1.2 mg/kg, levodopa/carbidopa: 80/20 mg/kg/day), an increase in embryo-fetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day when administered in combination with levodopa/carbidopa (approximately 7 and 13 times, respectively, the plasma rasagiline AUC at the MRHD). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone (1/1 times the MRHD on a mg/m² basis) 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.

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PART III: CONSUMER INFORMATION

AZILECT® (rasagiline mesylate tablets)

This leaflet is part of the "Product Monograph" published when AZILECT® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AZILECT®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Your physician has prescribed AZILECT (rasagiline mesylate) 0.5 mg or 1 mg tablets. AZILECT relieves the signs and symptoms of Parkinson's disease as initial therapy for early disease and as add-on therapy to dopamine agonists in early stages or levodopa in more advanced stages of the disease.

Before you begin using AZILECT, make sure you understand all the information provided about its possible benefits and risks. If you do not understand any of the information provided, contact your doctor for further clarification.

What it does:

AZILECT is used to treat the signs and symptoms of Parkinson's disease as monotherapy (without levodopa) or as adjunct therapy (with dopamine agonists or levodopa).

Parkinson's disease is a disorder of the central nervous system caused by a lack of dopamine – a substance in the brain used to send messages to your muscles to make them move. AZILECT belongs to a class of drugs called monoamine oxidase B inhibitors. AZILECT works by blocking the breakdown of dopamine in the brain.

When it should not be used:

Do not use AZILECT if you:

- are allergic to it or any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction (e.g., skin rash, hives) or any severe or unusual side effects.
- have moderate-to severe liver disease

Do not use AZILECT if you are taking any of the following medications:

- Cyclobenzaprine (a tricyclic muscle relaxant)
- Demerol (meperidine, pethidine)
- Dextromethorphan (an over-the-counter cough suppressant)

- Other MAO inhibitors for the treatment of Parkinson's disease or for any other indication
- Pain medications (notably tramadol, methadone, and propoxyphene)
- St. John's Wort

What the medicinal ingredient is:

The active substance is rasagiline. Each tablet contains 0.5 mg or 1 mg rasagiline (as mesylate).

What the nonmedicinal ingredients are:

Each AZILECT tablet also contains the following inactive ingredients: colloidal silicon dioxide, mannitol, starch, pregelatinized starch, stearic acid and talc.

What dosage forms it comes in:

AZILECT tablets are white to off-white, round, flat, bevelled tablets, marked with "GIL 0.5" on one side and plain on the other side for the 0.5 mg tablet or "GIL 1" on one side and plain on the other side for the 1 mg tablet.

WARNINGS AND PRECAUTIONS

Some people feel sleepy, drowsy, or, rarely, may suddenly fall asleep without warning (i.e. without feeling sleepy or drowsy) when taking AZILECT. During treatment with AZILECT take special care when you drive or operate a machine. If you experience excessive drowsiness or a sudden sleep onset episode, refrain from driving and operating machines, and contact your physician.

Before you use AZILECT, tell your doctor if you:

- are taking any antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic or tetracyclic antidepressants [e.g. Prozac (fluoxetine), Luvox (fluvoxamine) Zoloft (sertraline), Paxil (paroxetine), Celexa (citalopram) and Effexor (venlafaxine) and Remeron (mirtazapine)]
- are also taking levodopa, as there is the possibility of increased difficulty with movement. Your doctor may lower the dose of your levodopa therapy.
- have mild liver disease. Your dose may be reduced to 0.5 mg/day.
- are under the age of 18.
- are pregnant or planning to become pregnant. AZILECT should be used during pregnancy only if clearly needed.
- are breast-feeding

Wait at least 2 weeks after stopping tricyclic, tetracyclic, triazolopyridine, SSRI, or SNRI antidepressant treatment before starting treatment with AZILECT.

Wait at least 5 weeks after stopping fluoxetine treatment

before starting treatment with AZILECT.

AZILECT may be taken if you have mild kidney disease but should not be taken if you have moderate to severe kidney impairment.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. Therefore, your doctor should perform periodic skin examinations.

It is also important to tell your doctor before beginning treatment if:

- you drive or operate machinery
- you or your family member/caregiver notices you are developing urges to gamble, increased sexual urges, excessive eating or spending, and/or other intense urges that could harm yourself or others. These behaviors are called impulse control disorders. Your doctor may need to review your treatments.

INTERACTIONS WITH THIS MEDICATION

See the **DO NOT TAKE AZILECT** section for important safety information about drugs not to use at the same time as AZILECT.

Please ask your doctor or pharmacist for advice if you are taking or have recently taken any other medicines, even those obtained without a prescription. AZILECT may interact with the following medications or you might require a dose adjustment:

- Antidepressants
- Ciprofloxacin (an antibiotic) or other CYP1A2 inhibitors - if you take the antibiotic ciprofloxacin or other CYP1A2 inhibitors you should use 0.5 mg daily of AZILECT.
- Demerol (meperidine) or some other pain medications
- Dextromethorphan (an over-the-counter anti-cough drug)
- Levodopa – levodopa dose may be reduced
- Other MAOIs (monoamine oxidase inhibitors)
- Sympathomimetic amines including amphetamines, some decongestants, cold remedies, and weight loss products

PROPER USE OF THIS MEDICATION

Usual dose:

Take AZILECT exactly as instructed by your doctor. You

should talk with your doctor or pharmacist if you are unsure.

The recommended dose of AZILECT is 0.5 mg or 1 mg taken orally once daily either with or without food. Your doctor will determine which dose is appropriate for you.

Do not take more than the maximum recommended daily dose of 1 mg. Taking more than 1 mg may cause serious side effects which could include a severe headache, seizures, and a sudden rise in blood pressure. Should you experience these side effects seek immediate emergency medical assistance. For any other unusual symptoms you have not had before, call your doctor immediately.

Overdose:

If you think that you may have taken too many AZILECT tablets, contact a hospital emergency department, the nearest Poison Control Centre or your doctor or pharmacist immediately. You may require medical attention even if there are no symptoms. Take the AZILECT carton/bottle with you to show the doctor or pharmacist.

Missed Dose:

If you have forgotten to take a dose of AZILECT take the next dose at the usual time. Do not take a double dose to make up for the one you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AZILECT can have side effects.

The most commonly observed side effects that occurred in patients receiving AZILECT as monotherapy are: headache, flu-like symptoms, musculoskeletal pain, joint pain, depression, urinary urgency, indigestion and falls.

In patients receiving AZILECT as adjunct to dopamine agonist or levodopa therapy the most common side effects are: lack of coordination, accidental injury, weight loss, posture-dependant low blood pressure, vomiting, loss of appetite, joint pain, abdominal pain, nausea, constipation, dry mouth, rash, bruising, trouble sleeping, hands and legs swelling, and abnormal skin sensation.

AZILECT may cause hallucinations. Tell your doctor immediately if this happens to you while taking AZILECT.

Taking more than 1 mg may cause serious side effects which could include a severe headache, seizures, and a sudden rise in blood pressure. Should you experience these side effects seek immediate emergency medical assistance. For any other unusual symptoms you have not had before or are not mentioned here, contact your doctor or pharmacist immediately.

Serious side effects could result when taking AZILECT together with other medications. Therefore, please ask your doctor or pharmacist for advice if you are taking or have recently taken any other medicines, even those obtained without a prescription. Serious reactions (coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse), and sometimes fatal reactions could occur if you take AZILECT together with Demerol (meperidine) or some other pain medications (tramadol, methadone, tapentadol, and propoxyphene). Serious reactions (brief episodes of psychosis or bizarre behavior) could occur if you take AZILECT together with dextromethorphan (an over-the-counter anti-cough drug). Taking AZILECT together with other MAOIs (monoamine oxidase inhibitors) increases the risk of serious reactions such as hypertensive crisis.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk to your doctor, nurse or pharmacist		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Dyskinesia: difficulty performing common movements	√		
COMMON Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing	√		
Angina pectoris: Chest pain			√
Balance disorder, fall	√		
Hallucinations: Seeing, hearing or sensing things that are not real	√		
Decreased White Blood Cells: infections, fatigue, fever, cough, runny nose, aches and pains, Flu-like symptoms	√		
Dystonia: prolonged muscle contractions	√		
Skin cancer: irregular or		√	

new skin lesions			
UNCOMMON Stroke: numbness, weakness, confusion, blurred vision			√
Heart attack: chest pain often associated with left shoulder or jaw pain, feeling of constriction around chest and sweating			√
Hypotension: Low blood pressure that makes you feel dizzy or faint especially when getting up from a lying or sitting position		√	
UNKNOWN Serotonin syndrome: a combination of symptoms possibly including confusion, fever, headaches, blood pressure and pulse alterations, muscle twitching.			√
Hypertensive crisis: severe headache, seizures, confusion, excessively elevated blood pressure.			√
Feeling sleepy, drowsy, suddenly falling asleep without warning.		√	
Compulsive behaviour: urges to gamble, increased sexual urges, excessive eating and spending or any other abnormal behaviour.		√	

This is not a complete list of side effects. For any unexpected effects while taking AZILECT, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.
Store at room temperature (15-30° C).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at**
www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
 - **Fax toll-free to 1-866-678-6789**
 - **Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

www.tevacanadainnovation.com

or by contacting the sponsor, Teva Canada Innovation at:
1-866-530-6065

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