Rationale for Rational Polypharmacy in the Management of PD

Parkinson’s disease (PD) is a progressive, neurodegenerative disorder involving multiple peripheral and central neuronal pathways. Although the clinical management of PD is multifaceted, the 4 cardinal features of PD (bradykinesia, rigidity, tremor at rest, and postural instability) are directly related to the loss of striatal dopamine. Therefore, managing dopamine is recognized as the most effective way of treating the motor symptoms of PD.

Dopaminergic activity can be increased by several pathways, including providing dopamine from an external source; enhancing the activity of endogenous and exogenous dopamine by the inhibition of monamine oxidase (MAO) in the brain and catechol-O-methyltransferase (COMT) in the periphery; and by the use of medications that act directly on postsynaptic receptors and make metabolic conversion, storage, and release unnecessary. Agents currently approved for use as monotherapy in the treatment of newly diagnosed PD include carbidopa/levodopa (CD/LD), dopamine agonists, and the monoamine oxidase type B (MAO-B) inhibitor, rasagiline.

Due to the progressive degenerative nature of PD, patients experience an ongoing loss of dopaminergic neurons and dopamine, which results in worsening symptoms that may be difficult to control with monotherapy. One possible approach to address a loss of symptomatic control is to titrate the dose of the initial monotherapy agent. An alternative approach to consider is rational polypharmacy. Using this approach, the dose of the current agent is maintained and a second agent with a complementary mechanism of action is added. This method offers potential benefits and may provide a means of optimizing symptomatic control, while concurrently managing potential side effects.

“…consider…rational polypharmacy, … [in which] the dose of the current agent is maintained and a second agent with a complementary mechanism of action is added…and [which] may provide a means of optimizing symptomatic control, while concurrently managing potential side effects.”

Dopamine Agonists in Progressing PD

Dopamine agonists exert their effect by mimicking dopamine activity at the postsynaptic dopamine receptor. As PD progresses, continued loss of dopaminergic neurons and dopamine results in worsening symptoms that may be difficult to control with monotherapy, and patients taking a dopamine agonist may experience a less robust symptomatic response to the prescribed dose than they had previously. Rather than presumptively titrating the dopamine agonist dose, one may consider polypharmacy and add a second agent with a complementary mechanism of action, such as an MAO-B inhibitor or LD. This approach may provide a means of optimizing symptomatic control, while concurrently managing potential side effects.
Rationale for Rational Polypharmacy in the Management of PD

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Dopamine Agonists to Delay LD Initiation

Results of the O56 study showed that patients with early PD who initiated dopaminergic treatment with ropinirole versus LD had a significantly lower risk of dyskinesia (hazard ratio for remaining dyskinesia free, 2.82; 95 percent confidence interval [95% CI], 1.78 to 4.44; \( P < 0.001 \)) and a significantly longer time to dyskinesia onset (25% of patients with dyskinesia, 214 weeks and 104 weeks, respectively).

A 5-year post-hoc analysis and a 10-year follow-up to this study found that the delay observed in the emergence of LD-associated motor complications was related to the deferred initiation of LD treatment. These findings are important to consider when determining treatment strategies for patients with early PD because higher LD doses are associated with a greater incidence of dyskinesia; and chronic LD therapy is associated with end-of-dose “wearing off,” manifested as fluctuations in motor and nonmotor symptoms.

The ELLDOPA (Earlier versus Later Levodopa) study showed that use of LD is associated with a greater frequency of dyskinesia and “wearing off” (Figure 1). In patients who initiated antiparkinsonian treatment with LD monotherapy, initial loss of symptomatic control may first become apparent as end-of-dose wearing off, which manifests as fluctuations in motor and nonmotor symptoms. Similar to the management approach used with dopamine agonists, a common clinical strategy to address this problem has been to titrate the LD dose. A post-hoc analysis of the STRIDE-PD study data, however, has found that the risks of developing dyskinesia and wearing off increase significantly at LD doses >400 mg/d (Figure 3).

Levodopa in Progressing PD

Levodopa has been the standard treatment for managing the motor symptoms of PD for several decades. In the ELLDOPA study, LD significantly reduced the worsening of symptoms in a dose-response pattern in previously untreated patients with PD (Figure 2).

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**Figure 1.** Higher Levodopa Doses Were Associated With Increased “Off” Time and Dyskinesia in Previously Untreated Patients With Parkinson’s Disease in the ELLDOPA Study

![Graph showing percentage of patients in different treatment groups with “wearing off” and dyskinesia.

ELLDOPA indicates Earlier versus Later Levodopa.


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**Figure 2.** Changes in Total UPDRS Score With Levodopa Were Dose-Dependent in the ELLDOPA Study

![Graph showing changes in total UPDRS score with levodopa dose in the ELLDOPA study.

STRIDE-PD indicates STalevo Reduction In Dyskinesia Evaluation in Parkinson’s Disease.

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**Figure 3.** A Post-hoc Analysis of STRIDE-PD Study Data Found the Risks of Developing Dyskinesia and Wearing Off Increased in a Dose-Dependent Manner (\( P < 0.001 \) for each)

![Graph showing percentage of patients with “wearing off” and dyskinesia at different levodopa doses.

STRIDE-PD indicates STalevo Reduction In Dyskinesia Evaluation in Parkinson’s Disease.

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continued on page 4
Use of AZILECT® (rasagiline tablets) as Adjunct Therapy to Dopamine Agonists Without Levodopa in Patients With Parkinson’s Disease

AZILECT is a selective monoamine oxidase type B (MAO-B) inhibitor that was initially approved by the Food and Drug Administration (FDA) in 2006 for the treatment of the signs and symptoms of idiopathic Parkinson’s disease (PD) as monotherapy and as adjunct to levodopa (LD). Recently, the FDA has approved the expansion of the AZILECT indication to include adjunct therapy to dopamine agonists at a dose of 1 mg once daily. Thus, “AZILECT® (rasagiline tablets) is indicated for the treatment of Parkinson’s disease (PD).” This expanded indication is reflective of the established effectiveness of AZILECT for the treatment of PD throughout all stages of PD (early through advanced), as initial monotherapy or adjunct therapy.

This expanded indication was supported by the ANDANTE (Add-on to Dopamine Agonists in early-stage patients Needing enhanced Treatment Efficacy) study, an 18-week, randomized, double-blind, placebo-controlled study designed to determine the clinical efficacy, safety, and tolerability of once-daily AZILECT as add-on therapy to dopamine agonists in patients with early PD. Patients were eligible for study entry if they were taking a stable dose of dopamine agonist (ropinirole ≥6 mg/d or pramipexole ≥1.0 mg/d) for ≥30 days and ≤5 years, and their PD symptoms were no longer sufficiently controlled.

In the ANDANTE study…”[p]atients who received AZILECT experienced a significantly greater improvement in Total UPDRS score relative to placebo.”

In this trial, 326 patients were randomly assigned to receive placebo (n=164) or AZILECT 1 mg/d (n=162) in addition to their existing dose of dopamine agonist. The average PD duration at baseline was approximately 2 years (range 0.1 to 14.5 years); and the mean±SD dosages of ropinirole and pramipexole were 8.0±4.8 mg/d and 1.5±0.9 mg/d, respectively. The modified intent-to-treat (mITT) population, defined as all randomized patients who took ≥1 dose of study drug and had both a baseline and ≥1 postbaseline efficacy assessment, was used for efficacy analyses (AZILECT, n=159; placebo, n=162). The primary efficacy measure was the change from baseline in Total Unified Parkinson's Disease Rating Scale (UPDRS) score, which includes measures of motor function, activities of daily living, and mentation. Patients who received AZILECT experienced a significantly greater improvement in Total UPDRS score relative to placebo (Figure 1). No differences in effectiveness based on age or gender were detected between the 2 treatment groups.

Once-daily AZILECT used as adjunct to dopamine agonist therapy was associated with a low discontinuation rate due to adverse events, AEs: 8% for AZILECT versus 4% for placebo. AEs associated with AZILECT when used as add-on to dopamine agonist therapy are shown in the Table. The most commonly observed AEs were those in which the treatment difference for the incidence in AZILECT-treated patients was ≥3% higher than the incidence in placebo-treated patients. These included peripheral edema, fall, arthralgia, cough, and insomnia. Somnolence was also reported frequently; however, there was no difference in incidence rate between treatment groups (7% each).

**Figure 1. Change in Total UPDRS Score in Patients Receiving AZILECT as Adjunct to Stable Dopamine Agonist Therapy**

<table>
<thead>
<tr>
<th>Mean Change (±SE) From Baseline in UPDRS Total at Week 18</th>
<th>Placebo (n=162)</th>
<th>AZILECT 1 mg/d (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–1.2</td>
<td>–3.6*</td>
<td></td>
</tr>
</tbody>
</table>

Mean change from baseline. AZILECT –3.6 units vs placebo –1.2 units. Effect size AZILECT vs. placebo: –2.4 units (95% CI, –4.3 to –0.5). *P<0.012.

**Table. ANDANTE: Adverse Events* (AEs) Associated With AZILECT 1 mg as Add-on to Dopamine Agonist**

<table>
<thead>
<tr>
<th>AE</th>
<th>AZILECT 1 mg/d % of patients (n=159)</th>
<th>Placebo % of patients (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fall</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Discontinuation due to AE: AZILECT 1 mg/d = 8%; placebo = 4%.

As a selective MAO-B inhibitor, AZILECT irreversibly blocks the breakdown of dopamine. As add-on therapy to dopamine agonists, AZILECT enhances dopaminergic activity by preserving endogenous dopamine and provides a mechanism of action complementary to that of the dopamine agonists, which mimic the activity of dopamine at the postsynaptic receptor.
Use of AZILECT® (rasagiline tablets) as Adjunct Therapy to Dopamine Agonists Without Levodopa in Patients With Parkinson’s Disease

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During the clinical development of AZILECT, 1,523 patients with PD received AZILECT as initial monotherapy, as adjunct therapy to dopamine agonists, or as adjunct therapy to levodopa. In the PRESTO (Parkinson’s Rasagiline: Efficacy & Safety in the Treatment of Off) and LARGO (Lasting Effect in Adjunct Therapy With Rasagiline Given Once Daily) studies, up to 65% of patients using AZILECT as add-on therapy to LD were also taking a dopamine agonist. The ANDANTE study adds to this base of evidence and supports an expanded indication by demonstrating the benefits of AZILECT as first add-on to dopamine agonist therapy during a double-blind, placebo-controlled, randomized, clinical study.

Specifically, the ANDANTE study shows that adding AZILECT to a dopamine agonist regimen provides another option for symptom control before adjusting the dopamine agonist dose or adding LD. Furthermore, results from ANDANTE demonstrate that adding once-daily AZILECT to stable dopamine agonist regimens does not adversely affect safety and tolerability. Thus, the results of the ANDANTE trial and the expanded indication provide additional evidence supporting the benefits of treatment with AZILECT throughout the course of PD.

References:

“[T]he results of the ANDANTE trial and the expanded indication provide additional evidence supporting the benefits of treatment with AZILECT throughout the course of PD.”

Rationale for Rational Polypharmacy in the Management of PD

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Thus, as an alternative to increasing the LD dose, rational polypharmacy utilizing an agent with a complementary mechanism of action, such as an MAO-B inhibitor or dopamine agonist, may optimize symptomatic control while maintaining a lower dose of LD, which may help manage the potential risk of dyskinesia.

In summary, regardless of the initial therapeutic agent used, the judicious combination of 2 or more agents with complementary mechanisms of action may provide beneficial clinical outcomes and manage potential side effects for patients with progressing PD.

References:

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INDICATION
AZILECT® (rasagiline tablets) is indicated for the treatment of Parkinson’s disease (PD).

IMPORTANT SAFETY INFORMATION

• AZILECT is contraindicated with meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, cyclobenzaprine, or another (selective or non-selective) MAOI.
• Exacerbation of hypertension may occur during treatment with AZILECT. Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting AZILECT.
• Dietary tyramine restriction is not required during treatment with recommended doses of AZILECT. However, patients should be advised to avoid foods containing a very high amount of tyramine because of the potential for severe increases in blood pressure, also referred to as hypertensive urgency, crisis, or emergency.
• Concomitant use of AZILECT and antidepressants is not recommended; serotonin syndrome has been reported with concomitant use with an antidepressant or MAO inhibitors.
• Patients treated with AZILECT and other dopaminergic medications have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles. Prescribers should monitor patients for drowsiness or sleepiness.
• Patients with moderate to severe hepatic impairment should not take AZILECT. AZILECT should not exceed 1 mg/day or 0.5 mg/day for patients with mild hepatic impairment or in patients using ciprofloxacin or another CYP1A2 inhibitor.
• Patients receiving AZILECT with adjunct therapy have reported orthostatic hypotension, especially in the first two months of treatment.
• Dyskinesia (or exacerbations of dyskinesia), hallucinations or psychotic-like behavior, impulse control or compulsive behaviors, withdrawal-emergent hyperpyrexia/confusion, and melanoma are potentially associated with AZILECT.
• The most common side effects as monotherapy (AZILECT 1 mg, placebo, respectively [%]) include flu syndrome (5, 1), arthralgia (7, 4), depression (5, 2), and dyspepsia (7, 4).
• The most common side effects as adjunct to dopamine agonists (AZILECT 1 mg, placebo, respectively [%]) include peripheral edema (7, 4), fall (6, 1), arthralgia (5, 2), cough (4, 1), and insomnia (4, 1).
• The most common side effects as adjunct to levodopa therapy (AZILECT 1 mg, 0.5 mg, and placebo, respectively [%]) include dyskinesia (18, 18, 10), accidental injury (12, 8, 5), weight loss (9, 2, 3), postural hypotension (9, 6, 3), vomiting (7, 4, 1), anorexia (5, 2, 1), arthralgia (8, 6, 4), abdominal pain (5, 2, 1), nausea (12, 10, 8), constipation (9, 4, 5), dry mouth (6, 2, 3), rash (6, 3, 3), abnormal dreams (4, 1, 1), fall (11, 12, 8), and tenosynovitis (3, 1, 0).

Please see full Prescribing Information.
Q: Please describe the ANDANTE study.
A: The ANDANTE study was a Phase 4, double-blind, placebo-controlled, randomized trial that provided Class 1 evidence that the addition of AZILECT® (rasagiline tablets) to dopamine agonist monotherapy provides additional symptomatic benefit. At study entry, patients had Parkinson’s disease (PD) for an average of 2 years, and were having impaired symptom control despite dopamine agonist monotherapy. Patients remained on a stable dopamine agonist dose, were randomized to receive either placebo or AZILECT 1 mg per day, and then followed for 18 weeks. The primary efficacy endpoint was change from baseline in Total Unified Parkinson’s Disease Rating Scale (UPDRS) score in the AZILECT group compared with placebo. After 18 weeks, patients randomized to the AZILECT arm had a significant improvement in symptom control as measured by the Total UPDRS score.

Q: How does the ANDANTE study reinforce the idea of rational polypharmacy?
A: Rational polypharmacy means trying to manage patients throughout the duration of PD by using multiple medications with different mechanisms of action. Dopamine agonists mimic dopamine by binding directly to the postsynaptic dopamine receptor. AZILECT is an irreversible monoamine oxidase type B (MAO-B) inhibitor and blocks the breakdown of dopamine, augmenting the amount of dopamine available at the synaptic level. In the ANDANTE trial, we were able to show that a rational polypharmacy regimen consisting of AZILECT as add-on to dopamine agonist monotherapy resulted in an improvement in symptom control without adversely affecting safety or tolerability.

Q: How do you identify a patient on a dopamine agonist who needs additional symptom control?
A: Patients on dopamine agonist monotherapy may have re-emergence of symptoms over time. This has to be addressed by trying to adjust the dose of the dopamine agonist or by adding another medication. Instead of increasing the dopamine agonist dose, the clinician might consider adding AZILECT to dopamine agonist monotherapy because it provides additional symptom control while potentially managing side effects, and offers another option prior to adding levodopa.

Q: How does ANDANTE influence the way you treat your patients?
A: The ANDANTE study showed that by adding AZILECT to dopamine agonist monotherapy, we can improve symptom control with demonstrated tolerability. This helps us in the clinical setting when we have to make a decision to raise the dopamine agonist dose, add levodopa, or add AZILECT to dopamine agonist monotherapy. Good medical decision-making includes the use of evidence-based studies to help determine which option is the best one for each individual patient. With the results of the ANDANTE trial, we now have evidence that using a rational polypharmacy treatment strategy and adding AZILECT to dopamine agonist monotherapy can improve symptom control.

Q: As an investigator on the ANDANTE trial, can you provide any insight or thoughts from that perspective?
A: We had patients in our clinic who were on dopamine agonist monotherapy and needed greater symptom control; but, for a variety of reasons, we were not able to further increase the dopamine agonist dose. These patients were enrolled in ANDANTE and followed for 18 weeks. We were somewhat surprised at the end to see that those patients who had AZILECT had improved symptom control with demonstrated tolerability compared to the placebo group. This demonstrated that the treatment strategy of rational polypharmacy may have clinical implications, and that the addition of a drug with a different, complementary, mechanism of action might give added symptom benefit.

Dr. Isaacson is a consultant to and has received honoraria from Teva Neuroscience, Inc.
Supporting your treatment decision

Let Parkinson’s Support Solutions® help to make the most of the therapy you prescribed. We’ll provide patients with the support, education, and resources they need to better manage their disease.

PERSONALIZED SUPPORT
Our trained representatives are just a phone call away and are ready to answer nonmedical questions and provide information.

EDUCATIONAL MATERIALS
Parkinson’s Support Solutions can provide accurate and balanced educational materials on a variety of Parkinson’s disease-related topics.

FINANCIAL RESOURCES
Keeping AZILECT® (rasagiline tablets) affordable for your patients is important—we offer a number of resources to help.

THERE ARE 3 EASY WAYS TO GET YOUR PATIENTS STARTED:
1. Complete the registration form from your Teva representative and obtain the patient signature in your office, then fax to 1-866-920-0001
2. You or your patients can contact Parkinson’s Support Solutions directly by calling 1-866-880-8582
3. You or your patients can register online at www.parkinsonssupportsolutions.com

Please see Important Safety Information on page 5, and full Prescribing Information.
Rationale for Rational Polypharmacy in the Management of PD

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To learn more about the ANDANTE study and for the new indication for AZILECT® (rasagiline tablets), please visit www.ANDANTEstudy.com/PNV
AZILECT (rasagiline mesylate) Tablets for Oral Use

1. INDICATIONS AND USAGE

AZILECT® (rasagiline tablets) is indicated for the treatment of Parkinson's disease (PD).

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

When AZILECT is prescribed as monotherapy or as adjunct therapy in patients not taking levodopa, patients may start AZILECT at the recommended dose of 1 mg administered orally once daily. In patients taking levodopa, with or without other PD drugs (e.g., dopamine agonist, amantadine, anticholinergics), the recommended initial dose of AZILECT is 0.5 mg once daily. If the patient tolerates the daily 0.5 mg dose, but a sufficient clinical response is not achieved, the dose may be increased to 1 mg once daily. When AZILECT is used in combination with levodopa, a reduction of the levodopa dose may be considered, based upon individual response.

3. DOSAGE FORMS AND STRENGTHS

AZILECT 0.5 mg tablets (containing, as the active ingredient, rasagiline mesylate equivalent to 0.5 mg of rasagiline base) (3)

AZILECT 1 mg tablets (containing, as the active ingredient, rasagiline mesylate equivalent to 1 mg of rasagiline base) (3)

4. CONTRAINDICATIONS

Concomitant use of meperidine, tramadol, methadone, propoxyphene dextromethorphan, St. John's wort, cyclobenzaprine, or another (selective or non-selective) MAO inhibitor (4)

5. WARNINGS AND PRECAUTIONS

5.1 Hypertension

5.2 Serotonin Syndrome

5.3 Falling Asleep During Activities of Daily Living and Somnolence

5.4 Ciprofloxacin or Other CYP1A2 Inhibitors

5.5 Hepatic Impairment

5.6 Hypotension/Orthostatic Hypotension

5.7 Dyskinesia

5.8 Hallucinations/Psychotic-Like Behavior

5.9 Impulse Control/Compulsive Behaviors

5.10 Withdrawal-Emergent Hyperpyrexia and Confusion

5.11 Melanoma

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6.1 Clinical Trials Experience

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7.2 Dextromethorphan

7.3 MAO Inhibitors

7.4 Sympathomimetic Medications

7.5 Antidepressants

7.6 Ciprofloxacin or Other CYP1A2 Inhibitors

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8.2 Nursing Mothers

8.3 Pediatric Use

8.4 Geriatric Use

8.5 Hepatic Impairment

8.6 Renal Impairment

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9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10. OVERDOSE

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14. CLINICAL STUDIES

14.1 Monotherapy Use of AZILECT

14.2 Adjunct Use of AZILECT

15. HOW SUPPLIED/STORAGE AND HANDLING

16. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

AZILECT® (rasagiline tablets)

1. INDICATIONS AND USAGE

AZILECT (rasagiline tablets) is indicated for the treatment of Parkinson’s disease (PD).

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

When AZILECT is prescribed as monotherapy or as adjunct therapy in patients not taking levodopa, patients may start AZILECT at the recommended dose of 1 mg administered orally once daily.

In patients taking levodopa, with or without other PD drugs (e.g., dopamine agonist, amantadine, anticholinergics), the recommended initial dose of AZILECT is 0.5 mg once daily. If the patient tolerates the daily 0.5 mg dose, but a sufficient clinical response is not achieved, the dose may be increased to 1 mg once daily. When AZILECT is used in combination with levodopa, a reduction of the levodopa dose may be considered, based upon individual response.

3. DOSAGE FORMS AND STRENGTHS

AZILECT 0.5 mg Tablets: White to off-white, round, flat, beveled tablets, debossed with “GIL 0.5” on one side and plain on the other side containing, as the active ingredient, rasagiline mesylate equivalent to 0.5 mg of rasagiline base.

WARNINGs AND PRECAUTIONs

- May cause hypertension (including severe hypertensive syndromes) at recommended doses (5.1)
- May cause serotonin syndrome when used with antidepressants (5.2)
- May cause falling asleep during activities of daily living, daytime drowsiness, and somnolence (5.3)
- May cause hypotension, especially orthostatic (5.6)
- May cause or exacerbate dyskinesia. Decreasing the levodopa dose may lessen or eliminate this side effect (5.7)
- May cause hallucinations and psychotic-like behavior (5.8)
- May cause impulse control/compulsive behaviors (5.9)
- May cause withdrawal-emergent hyperpyrexia and confusion (5.10)
- Increased risk of melanoma: monitor patients for melanoma on a regular basis (5.11)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3% or greater than placebo):

- AZILECT monotherapy: flu syndrome, arthralgia, depression, dyspepsia (6.1)
- AZILECT used as adjunct without levodopa: peripheral edema, fall, arthralgia, cough, and insomnia (6.1)
- AZILECT used as adjunct to levodopa: dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anxiety, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, abnormal dreams, fall, and tenosynovitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Meperidine: Risk of serotonin syndrome (4, 7.1)
- Dextromethorphan: Risk of psychosis or bizarre behavior (4, 7.2)
- MAO inhibitors: Risk of non-selective MAO inhibition and hypertensive crisis (4, 7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Do not use AZILECT unless the potential benefit justifies the potential risk to the fetus (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2014

The recommended doses of AZILECT should not be exceeded because of risk of hypertension (see Warnings and Precautions (5.1)).

2.2 Patients Taking Ciprofloxacin or Other CYP1A2 Inhibitors

Patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should not exceed a dose of AZILECT 0.5 mg once daily [see Warnings and Precautions (5.4), Drug Interactions (7.6), and Clinical Pharmacology (12.3)].

2.3 Patients with Hepatic Impairment

Patients with mild hepatic impairment should not exceed a dose of AZILECT 0.5 mg once daily. AZILECT should not be used in patients with moderate or severe hepatic impairment [see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].
AZILECT® (rasagiline mesylate) Tablets for Oral Use

AZILECT 1 mg Tablets: White to off-white, round, flat, beveled tablets, debossed with “GIL 1” on one side and plain on the other side containing, as the active ingredient, rasagiline mesylate equivalent to 1 mg of rasagiline base.

4. CONTRAINDICATIONS
AZILECT is contraindicated for use with meperidine, tramadol, methadone, propoxyphene and MAO inhibitors (MAOIs), including other selective MAO-B inhibitors, because of risk of serotonin syndrome [See Warnings and Precautions (5.2)]. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with these medications. AZILECT is contraindicated for use with St. John's wort and with cyclosporine. AZILECT is contraindicated for use with dextromethorphan because of risk of epsode of psychosis or bizarre behavior.

5. WARNINGS AND PRECAUTIONS
5.1 Hypertension
Exacerbation of hypertension may occur during treatment with AZILECT. Medication adjustment may be necessary if elevation of blood pressure is sustained. Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting AZILECT.

In Study 3, AZILECT (1 mg/day) given in conjunction with levodopa, produced an increase in mean systolic blood pressure of 18 mm Hg compared to placebo (1%). Dietary tyramine restriction is not required during treatment with recommended doses of AZILECT. However, certain foods that may contain very high amounts (i.e., more than 150 mg) of tyramine that could potentially cause severe hypertension because of tyramine accumulation (including various clinical syndromes referred to as hypertension, urgency, crisis, or emergency in patients taking AZILECT, even at the recommended doses, due to increased sensitivity to tyramine. Patients should be advised to avoid foods containing a very large amount of tyramine while taking recommended doses of AZILECT because of the potential for large increases in blood pressure including clinical syndromes referred to as hypertensive urgency, crisis, or emergency. AZILECT is a selective inhibitor of MAO-B at the recommended doses of 0.5 or 1 mg daily. Selectivity for inhibiting MAO-B diminishes in a dose-related manner as the dose is progressively increased above the recommended daily doses.

5.2 Serotonin Syndrome
Serotonin syndrome has been reported concomitantly with antidepressant treatment (e.g., selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors-SNRIs, tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants) and a nonselective MAO (e.g., phenelzine, tranylcypromine) or selective MAO-B inhibitors, such as selegiline (Eldepryl) and rasagiline (AZILECT). Serotonin syndrome has also been reported concomitantly with concomitant use of AZILECT with meperidine, tramadol, methadone, or propoxyphene. AZILECT is contraindicated for use with meperidine, tramadol, methadone, propoxyphene and MAO inhibitors (MAOIs), including other selective MAO-B inhibitors [See Contraindications (4) and Drug Interactions (7.1)].

In the post-marketing surveillance data further suggest that orthostatic hypotension occurs most frequently in the first two months of AZILECT 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 while but supine. The risk for post-treatment hypotension (e.g., systolic <90 or diastolic <50 mm Hg) was significantly higher for AZILECT 1 mg (3.2%) compared to placebo (1.3%). There was no clear increased risk for lowering of blood pressure or postural hypotension associated with AZILECT 1 mg/day as monotherapy. When used as an adjunct to levodopa, levodopa hypotension was also reported as an adverse reaction in approximately 6% of patients treated with AZILECT 0.5 mg. 9% of patients treated with AZILECT 1 mg and 3% of patients treated with placebo. Postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in 1 patient (0.7%) patient treated with AZILECT 1 mg/day, no patients treated with AZILECT 0.5 mg/day and no placebo-treated patients.

When used as an adjunct to levodopa, AZILECT may cause dyskinesia or potentiate dopaminergic side effects and exacerbate pre-existing dyskinesia. In Study 3, the incidence of dyskinesia was 18% in patients treated with 0.5 mg or 1 mg AZILECT as an adjunct to levodopa and 10% for patients treated with placebo as an adjunct to levodopa. Decreasing the dose of levodopa may mitigate this side effect [see Adverse Reactions (6.7)].

5.8 Hallucinations/Psychotic-Like Behavior
In the monotherapy study (Study 1), the incidence of hallucinations reported as an adverse event was 1.3% in patients treated with AZILECT 1 mg and 0.7% in patients treated with placebo. In Study 1, the incidence of hallucinations reported as an adverse reaction and leading to drug discontinuation and premature withdrawal was 1.3% in patients treated with AZILECT 1 mg and 0% in placebo-treated patients. When studied as an adjunct therapy without levodopa (Study 2), hallucinations were reported as an adverse reaction in 1.2% of patients treated with 1 mg/day AZILECT 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 AZILECT 1 mg/day and in none of the placebo-treated patients. These patients showed somnolence while on AZILECT with other dopaminergic medications, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported more than 1-year after initiation of treatment. In Study 3, somnolence was a common occurrence in patients receiving AZILECT and was more frequent in patients with Parkinson's disease receiving AZILECT than in respective patients receiving placebo (8% AZILECT compared to 4% Placebo) [see Adverse Reactions (6.1)].

Before initiating treatment with AZILECT, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with AZILECT such as concomitant sedating medications, the presence of sleep disorders or concomitant use of certain plant medications that increase rasagiline plasma levels (e.g., ciprafolaxin) [see Drug Interactions (7.6)]. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., driving a motor vehicle, conversations, eating), AZILECT should be discontinued. If a decision is made to continue AZILECT, advise them to avoid driving and other potentially dangerous activities. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.4 Ciprofloxacin or Other CYP1A2 Inhibitors
Ciprofloxacin plasma concentrations may increase up to 2 fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. Patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should not exceed a dose of AZILECT 0.5 mg once daily [see Dosage and Administration (2.2), Drug Interactions (7.6), and Clinical Pharmacology (12.3)].
When studied as an adjunct to levodopa (Study 3), the incidence of hallucinations was approximately 3% in patients treated with AZILECT 0.5 mg/day, 4% in patients treated with AZILECT 1 mg/day, and 0% in placebo-treated patients (see Adverse Reactions (6.1)). 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 continue to develop, or a new and different abnormal thinking or psychiatric disorder may appear after starting AZILECT because of the risk of exacerbating the psychosis with an increase in central dopaminergic tone. In addition, many treatments for psychosis that decrease central dopaminergic tone may decrease the effectiveness of AZILECT (see Drug Interactions (7.8)). Consider dose reduction or stopping the medication if a patient develops hallucinations or psychotic-like behaviors while taking AZILECT.

5.9 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including AZILECT, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson’s disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with AZILECT. Consider dose reduction or stopping the medication if a patient develops such urges while taking AZILECT.

5.10 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone.

5.11 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 their caregivers are advised to monitor for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

6. ADVERSE REACTIONS

The following adverse reactions are described in more detail in the Warnings and Precautions section of the label:

- Hypertension (see Warnings and Precautions (5.1))
- Serotonin Syndrome (see Warnings and Precautions (5.2))
- Falling Asleep During Activities of Daily Living and Somnolence (see Warnings and Precautions (5.3))
- Hypotension/Orthostatic Hypotension (see Warnings and Precautions (5.6))
- Dyskinesia (see Warnings and Precautions (5.7))
- Hallucinations/Psychotic-Like Behaviors (see Warnings and Precautions (5.8))
- Impulse Control/Compulsive Behaviors (see Warnings and Precautions (5.9))
- Withdrawal-Emergent Hyperpyrexia and Confusion (see Warnings and Precautions (5.10))
- Melanoma (see Warnings and Precautions (5.11))

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the incidence of adverse reactions in the clinical trials of another drug and may not reflect the rates of adverse reactions observed in practice.

During the clinical development of AZILECT, Parkinson’s disease patients received AZILECT as initial monotherapy (Study 1) and as adjunct therapy (Study 2, Study 3, Study 4). As the populations in these studies 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, the adverse reactions are presented separately for each study.

Monotherapy Use of AZILECT

In Study 1, approximately 5% of the 149 patients treated with AZILECT discontinued treatment due to adverse reactions compared to 2% of the 151 patients who received placebo.

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

The most commonly observed adverse reactions in Study 1 (incidence in AZILECT-treated patients 3% or greater than the incidence in placebo-treated patients) included flu syndrome, arthralgia, depression, and dyspnea. Table 1 lists adverse reactions that occurred in 2% or greater of patients receiving AZILECT as monotherapy and were numerically more frequent than in the placebo group in Study 1.

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

Adjunct Use of AZILECT

AZILECT was studied as an adjunct therapy without levodopa (Study 2), or as an adjunct therapy to levodopa with some patients also taking dopamine agonists, COMT inhibitors, anticholinergics, or amantadine (Study 3 and Study 4).

In Study 2, approximately 8% of the 162 patients treated with AZILECT discontinued treatment due to adverse reactions compared to 4% of the 164 patients who received placebo.

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

The most commonly observed adverse reactions in Study 2 (incidence in AZILECT-treated patients 3% or greater than incidence in placebo-treated patients) included peripheral edema, fall, arthralgia, cough, and insomnia. Table 2 lists adverse reactions that occurred in 2% or greater in patients receiving AZILECT as adjunct therapy with- out levodopa and numerically more frequent than in the placebo group in Study 2.

Table 1: Adverse Reactions* in Study 1

<table>
<thead>
<tr>
<th>AZILECT 1 mg (N=149)</th>
<th>Placebo (N=161)</th>
<th>% of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Eczemasis</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neck Pain</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vertege</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Table 2: Adverse Reactions* in Study 2

<table>
<thead>
<tr>
<th>AZILECT 1 mg (N=162)</th>
<th>Placebo (N=164)</th>
<th>% of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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

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

In Study 3, adverse event reporting was considered more reliable than Study 4; therefore, only the adverse event data from Study 3 are presented below. In Study 3, 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 reactions, compared to 6% of the 159 patients who received placebo.

The adverse reactions that led to discontinuation of more than one patient were diarrhea, weight loss, hallucination, and rash.

The most commonly observed adverse reactions in Study 3 (incidence in AZILECT-treated patients 3% or greater than the incidence in placebo-treated patients) included dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anorexia,
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7.4 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 nonselective MAO inhibitors. Hypertensive crisis has been reported in patients taking the recommended dose of AZILECT and sympathomimetic medications. Severe hypertension has been reported in patients taking the recommended dose of AZILECT and ophthalmic drops containing sympathomimetic medications. 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.

7.5 Antidepressants
Concomitant use of AZILECT with one of many classes of antidepressants (e.g., SSRIs, SNRIs, triazolopyridine, tricyclic or tetracyclic antidepressants) is not recommended [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]. Concomitant use of AZILECT and MAO inhibitors is contraindicated [see Contraindications (4)].

7.6 Ciprofloxacin or 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. Patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should not exceed a dose of AZILECT 0.5 mg once daily [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].

7.7 Tyramine/Rasagiline Interaction
MAO in the gastrointestinal tract and liver (primarily type A) provides protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a tyramine reaction with hypertension including clinical syndromes referred to as hypertensive urgency, crisis, or emergency. Foods and medications containing large amounts of exogenous amines (e.g., from fermented cheese, herring, over-the-counter cough/cold medications) may cause release of norepinephrine resulting in a rise in systemic blood pressure. Results of a special tyramine challenge study indicate that rasagiline is selective for MAO-B at recommended doses and can be used without dietary tyramine restriction. However, certain foods may contain very high amounts (i.e., 150 mg or greater) of tyramine and could potentially cause a hypertensive reaction in individual patients taking AZILECT due to increased sensitivity to tyramine. 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 AZILECT treatment, in which most patients did not follow dietary tyramine restriction. There have been postmarketing reports of patients who experienced significantly elevated blood pressure (including rare cases of hypertensive crisis) after ingestion of unknown amounts of tyramine-rich foods while taking recommended doses of AZILECT. Patients should be advised to avoid foods containing a very large amount of tyramine while taking recommended doses of AZILECT [see Warnings and Precautions (5.1)].

7.8 Dopaminergic Antagonists
It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of AZILECT.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of rasagiline in pregnant women. AZILECT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a combined mating/fertility and embryo-fetal development study in pregnant rabbits, no effect on embryo-fetal development was observed at oral doses up to 3 mg/kg/day (approximately 30 times the plasma exposure (AUC) in humans 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 pregnant rats administered rasagiline (0.1, 0.3, 1 mg/kg/day) orally during gestation and lactation, offspring survival was decreased and offspring body weight was reduced at 0.3 mg/kg/day and 1 mg/kg/day (10 and 16 times the plasma AUC in humans at the MRHD). No plasma data were available at the no-effect dose (0.1 mg/kg); however, that dose is similar to the MRHD on a mg/m² basis. The effect of rasagiline 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 pregnant rats administered rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day) alone and in combination orally 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 rasagiline plasma AUC in humans at the MRHD and similar to the MRHD of levodopa/carbidopa [800/200 mg/day] on a mg/m² basis). In pregnant rabbits dosed orally 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.

Table 3: Adverse Reactions* in Study 3

<table>
<thead>
<tr>
<th>Reaction</th>
<th>AZILECT 1 mg (N=149) % of patients</th>
<th>AZILECT 0.5 mg (N=164) % of patients</th>
<th>Placebo (N=159) % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>18</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>12</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Fall</td>
<td>11</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Ataxia</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Neck pain</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sweating</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>3</td>
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<td>0</td>
</tr>
<tr>
<td>Dystonia</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Several of the more common adverse reactions seemed dose-related, including weight loss, postural hypotension, and dry mouth. There were no significant differences in the safety profile based on age or gender. During all Parkinson’s disease phase 2/3 clinical trials, the long-term safety profile was similar to that observed with shorter duration exposure.

7. Drug Interactions

7.1 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 (4)].

7.2 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 is contraindicated for use with AZILECT [see Contraindications (4)].

7.3 MAO Inhibitors
AZILECT is contraindicated for use with other MAO inhibitors because of the increased risk of nonselective MAO inhibition that may lead to a hypertensive crisis [see Contraindications (4)].
AZILECT® (rasagiline mesylate) Tablets for Oral Use

AZILECT® (rasagiline mesylate) Tablets for Oral Use

Rasagiline mesylate is a white to off-white powder, freely soluble in water or ethanol and sparingly soluble in isopropanol. Each AZILECT tablet for oral administration contains rasagiline mesylate equivalent to 0.5 mg or 1 mg of rasagiline base. Each AZILECT tablet also contains the following inactive ingredients: mannitol, starch, pregelatinized starch, colloidal silicon dioxide, stearic acid and talc.

11. DESCRIPTION
AZILECT® tablets contain rasagiline (as the mesylate), a propargylamine-based drug indicated for the treatment of idiopathic Parkinson’s disease. It is designated chemically as: 1H-Inden-1-amine, 2, 3-dihydro-N-2-propynyl-(1R)-, methanesulfonate. The empirical formula of rasagiline mesylate is (C₁₃H₁₇N)₂CH₂SO₄ and its molecular weight is 267.34.

Its structural formula is:

\[
\text{CH}_2\text{C} \quad \equiv \quad \text{CH}
\]

11.1. Mechanism of Action
AZILECT is a selective, irreversible MAO-B inhibitor indicated for the treatment of idiopathic Parkinson's disease. The results of a clinical trial designed to examine the effects of AZILECT on blood pressure when it is administered with increasing doses of levodopa/carbidopa are shown in Table 1. The results indicate that the combination of AZILECT and levodopa/carbidopa is safe and effective for the treatment of patients with Parkinson's disease.

11.2. Pharmacodynamics
Tyramine Challenge Test
Results of a tyramine challenge study indicate that rasagiline at recommended doses is relatively selective for inhibiting MAO-B and can be used without dietary tyramine restriction. However, certain foods (e.g., aged cheeses, such as Stilton cheese) may contain very high amounts of tyramine (i.e., 150 mg or greater) and could potentially cause severe hypertension caused by tyramine interaction in patients taking AZILECT due to mild increased sensitivity to tyramine at recommended doses. Relative selectivity of AZILECT for inhibiting MAO-B diminished in a dose-related manner as the dose progressively increased above the highest recommended daily dose (1 mg) [see Warnings and Precautions (5.1) and Drug Interactions (7.7)].

Platelet MAO Activity in Clinical Studies
Studies in healthy subjects and in Parkinson’s disease patients have shown that rasagiline is a substrate for 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 postdose. Multiple doses of rasagiline of 0.5, 1 and 2 mg per day resulted in complete MAO-B inhibition.

12. CLINICAL PHARMACOLOGY
12.1. Mechanism of Action
AZILECT is a selective, irreversible MAO-B inhibitor indicated for the treatment of idiopathic Parkinson's disease. The results of a clinical trial designed to examine the effects of AZILECT on blood pressure when it is administered with increasing doses of levodopa/carbidopa are shown in Table 1. The results indicate that the combination of AZILECT and levodopa/carbidopa is safe and effective for the treatment of patients with Parkinson's disease. The results of a clinical trial designed to examine the effects of AZILECT on blood pressure when it is administered with increasing doses of levodopa/carbidopa are shown in Table 1. The results indicate that the combination of AZILECT and levodopa/carbidopa is safe and effective for the treatment of patients with Parkinson's disease.

12.2. Pharmacodynamics
Tyramine Challenge Test
Results of a tyramine challenge study indicate that rasagiline at recommended doses is relatively selective for inhibiting MAO-B and can be used without dietary tyramine restriction. However, certain foods (e.g., aged cheeses, such as Stilton cheese) may contain very high amounts of tyramine (i.e., 150 mg or greater) and could potentially cause severe hypertension caused by tyramine interaction in patients taking AZILECT due to mild increased sensitivity to tyramine at recommended doses. Relative selectivity of AZILECT for inhibiting MAO-B diminished in a dose-related manner as the dose progressively increased above the highest recommended daily dose (1 mg) [see Warnings and Precautions (5.1) and Drug Interactions (7.7)].

Platelet MAO Activity in Clinical Studies
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12.3. Pharmacokinetics
Rasagiline in the range of 1-6 mg demonstrated a more than proportional increase in N-acetylvaline (NAC), while Cmax was dose proportional. Rasagiline 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 (Cmax) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%.

Food does not affect the Tmax of rasagiline, although Cmax 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.

Distribution
D (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.

13. ADVERSE REACTIONS
13.1. Clinical Trials
A postmarketing report described a single patient who developed a nonfatal serotonin syndrome after ingesting 100 mg of AZILECT in a suicide attempt. Another patient who was treated in error with 4 mg AZILECT daily and tramadol also developed a serotonin syndrome. One patient who was treated in error with 3 mg AZILECT daily experienced altered mental status and cardiovascular changes, which are consistent with serotonin syndrome.

A poison control center should be called for the most current treatment guidelines. A postmarketing report described a single patient who developed a nonfatal serotonin syndrome after ingesting 100 mg of AZILECT in a suicide attempt. Another patient who was treated in error with 4 mg AZILECT daily and tramadol also developed a serotonin syndrome. One patient who was treated in error with 3 mg AZILECT daily experienced altered mental status and cardiovascular changes, which are consistent with serotonin syndrome.

A poison control center should be called for the most current treatment guidelines.
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Drug-Drug Interactions

Levodopa
A study in Parkinson's disease patients, in which the effect of levodopa/carbidopa (LD/CD) on rasagiline pharmacokinetics at steady state was investigated, showed that the pharmacokinetics of rasagiline were not affected by concomitant administration of LD/CD.

Effect of Other Drugs on the Metabolism of AZILECT

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of rasagiline. There is the potential for inhibitors of this enzyme to alter AZILECT clearance when coadministered [see Dosage and Administration (2.2) and Warnings and Precautions (5.4)].

Ciprofloxacin: When ciprofloxacin, an inhibitor of CYP1A2, was administered to healthy volunteers (n=12) at 500 mg (BID) with rasagiline at 2 mg/day, the AUC of rasagiline increased by 83% and there was no change in the elimination half life to health subjects. Because 1-AI is not an MAO inhibitor, no dose adjustment is needed for patients with mild and moderate renal impairment. Data are not available for patients with severe renal impairment.

Elderly
Since age has little influence on rasagiline pharmacokinetics, it can be administered at the recommended dose in the elderly (>65 years).

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.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In mice, there was an increase in lung tumors (combined adenomas/carcinomas) at 15 and 45 mg/kg in males and females. At the lowest dose tested, plasma AUCs were approximately 5 times those expected in humans at the MRHD.

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

Mutagenesis
Rasagiline was reproductively 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 and in the in vivo micronucleus assay in mice. Rasagiline was also negative in the in vivo micronucleus assay in mice when administered in combination with levodopa/carbidopa.

Impairment of Fertility
Rasagiline had no effect on mating performance or fertility in rats treated prior to and throughout the mating period and continuing in females through gestation day 17 at oral doses of up to 3 mg/kg/day (approximately 30 times the plasma AUC in humans at the MRHD). The effect of rasagiline administered in combination with levodopa/carbidopa on mating and fertility has not been examined.

14. CLINICAL STUDIES

The effectiveness of AZILECT for the treatment of Parkinson's disease was established in four 18- to 26-week, randomized, placebo-controlled trials, as initial monotherapy or adjunct therapy.

14.1 Monotherapy Use of AZILECT

Study 1 was a double-blind, randomized, fixed-dose parallel group, 26-week study in early Parkinson's disease patients not receiving any concomitant dopaminergic therapy at the start of the study. The majority of the patients were not treated with medications for Parkinson's disease before receiving AZILECT.

In Study 1, 404 patients were randomly assigned to receive placebo (138 patients), AZILECT 1 mg/day (134 patients) or AZILECT 2 mg/day (132 patients). Patients were not allowed to take levodopa, dopamine agonists, selegiline or amantadine, but could take stable doses of anticholinergic medication, if necessary. The average Parkinson's disease duration was approximately 1 year (range 0 to 11 years).

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.

AZILECT (1 or 2 mg once daily) was superior to placebo on the primary measure of effectiveness in patients receiving six months of treatment and not on dopaminergic therapy. The effectiveness of AZILECT 1 mg and 2 mg was comparable. Table 4 shows the results of Study 1. There were no differences in effectiveness based on age or gender between AZILECT 1 mg/day and placebo.

Table 4: Change in Total UPDRS Score in Study 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline score</th>
<th>Change from baseline to termination score</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>24.5</td>
<td>3.9</td>
<td>---</td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>24.7</td>
<td>0.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>AZILECT 2 mg</td>
<td>25.9</td>
<td>0.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

14.2 Adjunct Use of AZILECT

Study 2 was a double-blind, randomized, placebo-controlled, parallel group, 18-week study, investigating AZILECT 1 mg as adjunct therapy to dopamine agonists without levodopa. Patients were on a stable dose of dopamine agonist (ropinirole, mean ± standard deviation 5.1 ± 0.8 mg/day) or pramipexole, mean ± standard deviation 1.5 mg/day) therapy for >30 days, but at doses not sufficient to control Parkinson's disease symptoms.

In Study 2, 321 patients randomly received placebo (162 patients) or AZILECT 1 mg/day (159 patients) and had a post-baseline assessment. 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 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)].

In Study 2, AZILECT 1 mg was superior to placebo on the primary measure of effectiveness (see Table 5).

Table 5: Change in Total UPDRS Score in Study 2

<table>
<thead>
<tr>
<th></th>
<th>Baseline score</th>
<th>Change from baseline to termination score</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>29.8</td>
<td>-1.2</td>
<td>---</td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>32.1</td>
<td>-3.6</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* A negative change from baseline indicates improvement in the UPDRS.

Secondary outcome assessment of the individual subscales of the UPDRS indicates that the UPDRS Part III motor subscale was primarily responsible for the overall AZILECT effect on the UPDRS score (see Table 6).

Table 6: Secondary Measures of Effectiveness in Study 2

<table>
<thead>
<tr>
<th></th>
<th>Baseline score</th>
<th>Change from baseline to termination score</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS ADL Part II (Activities of Daily Living) subscale score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7.9</td>
<td>0.4</td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>8.6</td>
<td>-0.3</td>
</tr>
<tr>
<td>UPDRS Part III Motor subscale score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>20.4</td>
<td>-1.2</td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>22.2</td>
<td>-3.7</td>
</tr>
</tbody>
</table>

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AZILECT® (rasagiline mesylate) Tablets for Oral Use

16. HOW SUPPLIED/STORAGE AND HANDLING

AZILECT 0.5 mg Tablets:
White to off-white, round, flat, beveled tablets, debossed with “GIL 0.5” on one side and plain on the other side. Supplied as bottles of 30 tablets (NDC 68546-142-56).

AZILECT 1 mg Tablets:
White to off-white, round, flat, beveled tablets, debossed with “GIL 1” on one side and plain on the other side. Supplied as bottles of 30 tablets (NDC 68546-229-56).

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

17. PATIENT COUNSELING INFORMATION

Hypertension
Advise patients that treatment with recommended doses of AZILECT may be associated with elevations of blood pressure. Tell patients who experience elevation of blood pressure while taking AZILECT to contact their healthcare provider.

The risk of using higher than recommended daily doses of AZILECT should be explained, and a brief description of the tyramine associated hypertensive reaction provided.

Advise patients to avoid certain 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. If patients eat foods very rich in tyramine and do not feel well soon after eating, they should contact their healthcare provider (see Warnings and Precautions (5.1)).

Serotonin Syndrome
Tell patients to inform their physician if they are taking, or planning to take, any prescription or over-the-counter drugs, especially antidepressants and over-the-counter cold medications, since there is a potential for interaction with AZILECT. Because patients should not use meperidine or certain other analgesics with AZILECT, they should contact their healthcare provider before taking analgesics (see Contraindications (4) and Warnings and Precautions (5.2)).

Falling Asleep During Activities of Daily Living and Somnolence
Advise and alert patients about the potential for sedating effects associated with AZILECT and other dopaminergic medications, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Because somnolence can be a frequent adverse reaction with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with AZILECT and other dopaminergic medications to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of AZILECT.

Because of possible additive effects, advise patients to exercise caution when patients are taking other sedating medications, alcohol, or other central nervous system depressants (e.g., benzodiazepines, antipsychotics, antidepressants) in combination with AZILECT or when taking concomitant medications that increase plasma levels of rasagiline (e.g., ciprofloxacin) (see Warnings and Precautions (5.3)).

Ciprofloxacin or Other CYPIA2 Inhibitors
Inform patients that they should contact their healthcare provider of AZILECT if they take ciprofloxacin or a similar drug that could increase blood levels of rasagiline because of the need to adjust the dose of AZILECT (see Dosage and Administration (2.2) and Warnings and Precautions (5.4)).

Table 9: Secondary Measures of Effectiveness in Study 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from baseline (hours)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.81</td>
<td></td>
</tr>
<tr>
<td>AZILECT 0.5 mg</td>
<td>-0.60</td>
<td></td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>-0.68</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Secondary Measures of Effectiveness in Study 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from baseline (hours)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.89</td>
<td></td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>-2.61</td>
<td></td>
</tr>
</tbody>
</table>

In Study 3 and Study 4, the dose reduction of levodopa was allowed within the first 6 weeks, if dopaminergic side effects developed including dyskinesia or hallucinations. In Study 3, the levodopa dose was reduced 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 AZILECT groups, respectively. When levodopa was reduced, the dose was reduced by 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In Study 4, levodopa dose reduction occurred in 6% of patients in the placebo group and in 9% in the AZILECT 1 mg/day group, respectively. When levodopa was reduced, it was reduced by 13% and 11% in the placebo and the AZILECT groups, respectively.

There were no differences in effectiveness based on age or gender between AZILECT 1 mg/day and placebo.

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 performed during an “ON” period. In both scales, a negative response represents improvement. Tables 9 and 10 show these results for Studies 3 and 4.

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Study 3 and Study 4 were randomized, multinational trials 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.). Study 3 was conducted in North America (U.S. and Canada) and compared AZILECT 0.5 mg and 1 mg daily to placebo. Study 4 was conducted outside of North America in Europe, Argentina and Israel, and compared AZILECT 1 mg daily to placebo.

Patients had Parkinson’s disease for an average of 9 years (range 5 months to 33 years), had taken levodopa for an average of 8 years (range 5 months to 32 years), and had motor fluctuations for approximately 3 to 4 years (range 1 month to 23 years). Patients kept home Parkinson’s disease 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, or “ON” with troublesome dyskinesia, “OFF” (period of relatively poor function and mobility) or asleep. “Troublesome” dyskinesia is defined as dyskinesia that interferes with the patient’s daily activity. All patients had at least one of their motor symptoms with motor fluctuations typical of advanced stage disease despite receiving levodopa/decarboxylase inhibitor. The average dose of levodopa taken with a decarboxylase inhibitor was approximately 700 to 800 mg (range 150 to 3000 mg/day). Patients continued their stable doses of additional anti-PD medications at entry into the trials. Approximately 65% of patients in both studies were also taking a dopamine agonist. In the North American study (Study 3), approximately 35% of patients took entacapone with levodopa/decarboxylase inhibitor. The majority of patients taking entacapone were also taking a dopamine agonist.

In Study 3 and Study 4, the primary outcome of effectiveness was the change in the mean number of hours spent in the “OFF” state at baseline compared to the mean number of hours spent in the “OFF” state during the treatment period. In Study 3, patients were randomly assigned to receive placebo (159 patients), AZILECT 0.5 mg/day (164 patients), or AZILECT 1 mg/day (149 patients) for 26 weeks. Patients averaged 6 hours daily in the “OFF” state at baseline as confirmed by home diaries.

In Study 4, patients were randomly assigned to receive placebo (229 patients), AZILECT 1 mg/day (231 patients) or a COMT inhibitor (active comparator), taken along with scheduled doses of levodopa/decarboxylase inhibitor (227 patients) for 18 weeks. Patients averaged 5.6 hours daily in the “OFF” state at baseline as confirmed by home diaries.

In Study 3 and Study 4, AZILECT 1 mg once daily reduced “OFF” time compared to placebo when added to levodopa in patients experiencing motor fluctuations (Tables 7 and 8). The lower dose (0.5 mg) of AZILECT also significantly reduced “OFF” time (Table 7), but was numerically smaller than the 1 mg dose of AZILECT. In Study 4, the active comparator also reduced “OFF” time when compared to placebo.

In Study 3 and Study 4, dose reduction of levodopa was allowed within the first 6 weeks, if dopaminergic side effects developed including dyskinesia or hallucinations. In Study 3, the levodopa dose was reduced 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 AZILECT groups, respectively. When levodopa was reduced, the dose was reduced by 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In Study 4, levodopa dose reduction occurred in 6% of patients in the placebo group and in 9% in the AZILECT 1 mg/day group, respectively. When levodopa was reduced, it was reduced by 13% and 11% in the placebo and the AZILECT groups, respectively. There were no differences in effectiveness based on age or gender between AZILECT 1 mg/day and placebo.

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 performed during an “ON” period. In both scales, a negative response represents improvement. Tables 9 and 10 show these results for Studies 3 and 4.

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Table 7: Change in mean total daily “OFF” time in Study 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (hours)</th>
<th>Change from baseline to treatment period (hours)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.0</td>
<td>-0.9</td>
<td>---</td>
</tr>
<tr>
<td>AZILECT 0.5 mg</td>
<td>6.0</td>
<td>-1.4</td>
<td>0.0199</td>
</tr>
<tr>
<td>AZILECT 1.0 mg</td>
<td>6.3</td>
<td>-1.9</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 8: Change in mean total daily “OFF” time in Study 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (hours)</th>
<th>Change from baseline to treatment period (hours)</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5.5</td>
<td>-0.4</td>
<td>---</td>
</tr>
<tr>
<td>AZILECT 1.0 mg</td>
<td>5.6</td>
<td>-1.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
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Hepatic Impairment
Tell patients who have hepatic problems to contact their healthcare provider regarding possible changes in AZILECT dosing [see Warnings and Precautions (5.5)].

Hypotension/Orthostatic Hypotension
Patients should be advised that they may develop orthostatic hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after weeks of treatment). Accordingly, patients should be cautioned against standing up rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially, at the initiation of treatment with AZILECT [see Warnings and Precautions (5.6)].

Dyskinesia
Advise patients taking AZILECT as adjunct to levodopa that there is a possibility of dyskinesia or increased dyskinesia [see Warnings and Precautions (5.7)].

Hallucinations/Psychotic-Like Behavior
Inform patients that hallucinations or other manifestations of psychotic-like behavior can occur when taking AZILECT. Advise patients that, if they have a major psychotic disorder, that AZILECT should not ordinarily be used because of the risk of exacerbating the psychosis. Patients with a major psychotic disorder should also be aware that many treatments for psychosis may decrease the effectiveness of AZILECT [see Warnings and Precautions (5.8)].

Impulse Control/Compulsive Behaviors
Advise patients that they may experience intense urges to gamble, increased sexual urges, other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease (including AZILECT). Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges, or other urges while being treated with AZILECT. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking AZILECT. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking AZILECT [see Warnings and Precautions 5.9].

Withdrawal-Emergent Hyperpyrexia and Confusion
Tell patients to contact their healthcare provider if they wish to discontinue AZILECT [see Warnings and Precautions (5.10)].

Missing Dose
Instruct patients to take AZILECT as prescribed. If a dose is missed, the patient should not double-up the dose of AZILECT. The next dose should be taken at the usual time on the following day.

Marketed by: TEVA Neuroscience, Inc., Overland Park, KS 66211
Distributed by: TEVA Pharmaceuticals USA, Inc., North Wales, PA 19454
AZI-40850