AZILECT® (rasagiline) Tablets

- 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).

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, anorexia, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, abnormal dreams, fall, and tenoynovitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 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. (8.1). See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

AZILECT, a monoamine oxidase (MAO)-B inhibitor (MAOBI), is indicated for the treatment of Parkinson's disease (1).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

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 on individual response.

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 (2.3, 5.5).

3 DOSAGE FORMS AND STRENGTHS

- AZILECT 0.5 mg tablets (3)
- AZILECT 1 mg tablets (3)

CONTRAINDICATIONS

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

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).

ADVERSE REACTIONS

- Constipation, dry mouth, rash, abnormal dreams, fall, and tenosynovitis (6.1).
- Postural hypotension, vomiting, anorexia, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, abnormal dreams, fall, and tenoynovitis (6.1).

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. (8.1).

PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION

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 on individual response.

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)].

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.

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.
AZILECT® (rasagiline) Tablets

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 cyclobenzaprine. AZILECT is contraindicated for use with dextromethorphan because of risk of episode 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 increased risk of post-treatment high blood pressure (e.g., systolic > 180 or diastolic >100 mm Hg) of 4% compared to 3% for placebo [see Adverse Reactions (6.1)]. When used as an adjunct to levodopa (Studies 3 and 4), the risk for developing post-treatment high blood pressure (e.g., systolic > 180 or diastolic >100 mm Hg) combined with a significant increase from baseline (e.g., systolic > 30 or diastolic > 20 mm Hg) was higher for AZILECT (2%) 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 interaction (including various clinical syndromes referred to as hypertensive 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. The effective 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 with concomitant use of an antidepressant (e.g., selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors-SNRIs, tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants) and a nonselective MAO inhibitor (e.g., phenelzine, tranylcypromine) or selective MAO-B inhibitors, such as selegiline (Edepryl) and rasagiline (AZILECT). Serotonin syndrome has also been reported with concurrent 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, 7.2, 7.3)].

In the post-marketing period, potentially life-threatening serotonin syndrome has been reported in patients treated with antidepressants concomitantly with AZILECT. Concomitant use of AZILECT with one of many classes of antidepressants (e.g., SSRIs, SNRIs, trazodone, tricyclic or tetracyclic antidepressants) is not recommended [see Drug Interactions (7.5)].

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, tachycardia, nausea, diarrhea), and somatic effects (e.g., muscular rigidity, myoclonus, muscle twitching, hyperreflexia manifested by clonus, and tremor). Seizures can result from serotonin syndrome. AZILECT clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with AZILECT. However, in the post-marketing period, potentially life-threatening serotonin syndrome has been reported in patients treated with antidepressants concomitantly with AZILECT. Clinical trial data further suggest that orthostatic hypotension occurs most frequently in the first two months of AZILECT treatment and tends to decrease over time.

5.3 Falling Asleep During Activities of Daily Living and Somnolence
Falling asleep while engaged in activities of daily living (ADL) in patients treated with AZILECT may occur. In clinical trials, the incidence of falling asleep while engaged in ADL was approximately 44% for AZILECT vs 33% for placebo for mild to moderate sleepiness. At the 1 mg dose, the frequency of orthostatic hypotension (at any time during the study) was approximately 44% for AZILECT vs 33% for placebo for mild to moderate sleepiness. The incidence of postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in one (0.7%) patient treated with AZILECT 1 mg/day, no patients treated with placebo. Postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in one (0.7%) patient treated with AZILECT 1 mg/day, no patients treated with AZILECT 0.5 mg/day and no placebo-treated patients.

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 (6% AZILECT compared to 4% Placebo) [see Adverse Reactions (6.1)].

When studied as an adjunct therapy without levodopa (Study 2), hallucinations were reported in patients treated with AZILECT than in respective patients treated with placebo (6% AZILECT compared to 4% Placebo) [see Adverse Reactions (6.1)].

5.4 Ciprofloxacin or Other CYP1A2 Inhibitors
Serotonin plasma concentrations may increase up to 2 fold in patients receiving 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 Dosage and Administration (2.2), Drug Interactions (7.6), and Clinical Pharmacology (12.3)].

5.5 Hepatic Impairment
Serotonin plasma concentrations may increase in patients with hepatic impairment. However, serotonin plasma concentrations with mild hepatic impairment should be given the dose of AZILECT 0.5 mg once daily. AZILECT should not be used in patients with moderate or severe hepatic impairment [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

5.6 Hypotension / Orthostatic Hypotension
In Study 3, the incidence of orthostatic hypotension consisting of a systolic blood pressure decrease (>30 mm Hg) or a diastolic blood pressure decrease (> 20 mm Hg) after standing was 13% with AZILECT (1 mg/day) compared to 9% with placebo [see Adverse Reactions (6.1)].

At the 1 mg dose, the frequency of orthostatic hypotension (at any time during the study) was approximately 44% for AZILECT vs 33% for placebo for mild to moderate sleepiness. The incidence of postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in one (0.7%) patient treated with AZILECT 1 mg/day, no patients treated with placebo (0.6%) [see Adverse Reactions (6.1)].

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

5.7 Dyskinesia
Serotonin plasma concentrations may increase in patients with hepatic impairment. However, serotonin plasma concentrations with mild hepatic impairment should be given the dose of AZILECT 0.5 mg once daily. AZILECT should not be used in patients with moderate or severe hepatic impairment [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

In Study 2, where AZILECT was given as an adjunct therapy in patients not taking levodopa, there were 5 reports of orthostatic hypotension in patients taking AZILECT 1 mg (3.1%) and 1 report in patients taking placebo (0.6%) [see Adverse Reactions (6.1)].

AZILECT® (rasagiline) Tablets

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 event and leading to drug discontinuation and premature withdrawal was 1.5% 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.

When studied as an adjunct to levodopa (Study 3), the incidence of hallucinations was approximately 5% in patients treated with AZILECT 0.5 mg/day, 4% in patients treated with AZILECT 1 mg/day, and 2% in patients treated with placebo.
AZILECT® (rasagiline) Tablets

The incidence of hallucinations leading to drug discontinuation and premature withdrawal was about 1% in patients treated with 0.5 mg AZILECT and 1 mg AZILECT/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, delirium, agitation, hallucinations, and delusions. [see Warnings and Precautions (5.6)]

Falling Asleep During Activities of Daily Living and Somnolence

Patients should be informed of the possibility of developing hallucinations and instructed to report them to their healthcare provider promptly should they develop. Patients with a major psychotic disorder should ordinarily not be treated with AZILECT because of the risk of exacerbating the psychosis with an increase in central dopaminergic tone. [see Warnings and Precautions (5.7)]

Fever

Gastroenteritis

Rhinitis

Arthritis

Echymosis

Malaise

Neck Pain

Paresthesia

Vertigo

Table 1: Adverse Reactions* in Study 1

<table>
<thead>
<tr>
<th>AZILECT 1 mg (N=149)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2</td>
</tr>
<tr>
<td>Malaise</td>
<td>2</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
</tr>
</tbody>
</table>

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

Table 2: Adverse Reactions* in Study 2

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

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

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 in placebo-treated patients) included dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anorexia, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, abnormal dreams, fall, and tenosynovitis.
Table 3: Adverse Reactions* in Study 3

<table>
<thead>
<tr>
<th></th>
<th>AZILECT 1 mg (N=149)</th>
<th>AZILECT 0.5 mg (N=164)</th>
<th>Placebo (N=159)</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>3</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>
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<tr>
<td>Abdominal pain</td>
<td>5</td>
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<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>
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<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>
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</tr>
<tr>
<td>Neck pain</td>
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<tr>
<td>Sweating</td>
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<tr>
<td>Tenosynovitis</td>
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<td>Dystonia</td>
<td>3</td>
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<tr>
<td>Gingivitis</td>
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<td>Hemorrhage</td>
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</tr>
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<td>Hernia</td>
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</tr>
<tr>
<td>Myasthenia</td>
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<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)].

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 hypertensive crisis has been reported in patients taking 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
M AO 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 agonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of AZILECT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risks associated with the use of AZILECT in pregnant women. In animal studies, oral administration of rasagiline to rats during gestation and lactation resulted in decreased survival and reduced body weight in the offspring at doses similar to those used clinically. When administered to pregnant animals in combination with levodopa/carbidopa, there were increased incidences of fetal skeletal variations in rats and increases in embryofetal death and cardiovascular abnormalities in rabbits [see Data].

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risks of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data
In a combined mating/fertility and embryofetal development study in pregnant rats, no effect on embryofetal 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, 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). The no-effect dose (0.1 mg/kg) for adverse developmental effects is similar to the MRHD on a body surface area (mg/m²) basis. The effect of rasagiline was not observed 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, 0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (30/20 mg/kg/day) (alone and in combination) orally throughout the period of organogenesis, there was an increased incidence of fetal skeletal variations in fetuses from rats treated with rasagiline in combination with levodopa/carbidopa.
AZILECT® (rasagiline) Tablets

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 embryofetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day when administered with levodopa/carbidopa (approximately 7 and 13 times, respectively, the rasagiline plasma AUC in humans at the MRHD). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone (similar to the MRHD on a mg/m² basis) and to a greater extent when rasagiline (at all doses; 1-13 times the rasagiline plasma AUC in humans at the MRHD) was administered in combination with levodopa/carbidopa.

8.2 Lactation

Risk Summary

There are no data on the presence of rasagiline in human milk or the effects on the breastfed infant. In rats, rasagiline was shown to inhibit prolactin secretion. The clinical relevance in humans is unknown, and there are no data on the effects of rasagiline on prolactin secretion or milk production in humans. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AZILECT and any potential adverse effects on the breastfed infant from AZILECT or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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 nongeriatric patients.

8.6 Hepatic Impairment

Rasagiline plasma concentration may be increased 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 (Child-Pugh score 10-15) hepatic impairment. Patients with mild hepatic impairment should not exceed a dose of 0.5 mg/day. AZILECT should not be used in patients with moderate or severe hepatic impairment [see Dosage and Administration (2.3), Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)].

8.7 Renal Impairment

Dose adjustment of AZILECT is not required for patients with mild or moderate renal impairment because AZILECT plasma concentrations are not increased in patients with moderate renal impairment. Rasagiline has not been studied in patients with severe renal impairment [see Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AZILECT is not a controlled substance.

9.2 Abuse

Studies conducted in mice and rats did not reveal any potential for drug abuse and dependence. Clinical trials have not revealed any evidence of the potential for abuse, tolerance, or physical dependence; however, systematic studies in humans designed to evaluate these effects have not been performed.

9.3 Dependence

Studies conducted in mice and rats did not reveal any potential for drug abuse and dependence. Clinical trials have not revealed any evidence of the potential for abuse, tolerance, or physical dependence; however, systematic studies in humans designed to evaluate these effects have not been performed.

10 OVERDOSAGE

In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg of AZILECT there were three reports of cardiovascular side effects (including hypertension and postural hypotension) which resolved following treatment discontinuation. Although no cases of overdose have been observed with AZILECT during the clinical development program, the following description of presenting symptoms and clinical course is based upon overdose descriptions of nonselective MAO inhibitors.

The signs and symptoms of nonselective MAOI overdose may not appear immediately. Delays of up to 12 hours after ingestion of drug and the appearance of signs may occur. The peak intensity of the syndrome may not be reached until for a day following the overdose. Death has been reported following overdose; therefore, immediate hospitalization, with continuous patient observation and monitoring for at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The severity of the clinical signs and symptoms of MAOI overdose varies and may be related to the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of MAOI overdose may include: drowsiness, diziness, 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.

There is no specific antidote for AZILECT overdose. The following suggestions are offered based upon the assumption that AZILECT overdose may be modeled after nonselective MAO inhibitor poisoning. Treatment of overdose with nonselective MAO inhibitors is symptomatic and supportive. Respiratory should be supported by appropriate measures, including maintenance 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 reduce the risk of hypertensive tyramine reaction.

A poison control center should be called for the most current treatment guidelines. A recent marketing report described a single patient who developed a nortriptyline-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 alternating episodes of vascular fluctuations consisting of hypertension and orthostatic hypotension.

11 DESCRIPTION

AZILECT® tablets contain rasagiline (as the mesylate), a propargylamine-based drug indicated for the treatment of idiopathic Parkinson’s disease. Rasagiline mesylate is designated chemically as: 1H-Inden-1-amine, 2, 3-dihydro-N-2-propynyl-, (1R),-methanesulfonate. The empirical formula of rasagiline mesylate is C₂₁H₂₀N₂O₄S and its molecular weight is 387.44.

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 0.5 mg or 1 mg of rasagiline (equivalent to 0.78 mg or 1.56 mg of rasagiline mesylate). Each AZILECT tablet also contains the following inactive ingredients: mannitol, starch, pregelatinized starch, colloidal silicon dioxide, stearic acid, and talc.

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 clonidine and levodopa in patients with idiopathic Parkinson’s disease, 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. 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 terminal, brain, liver and intestinal tissue. In vivo animal studies in brain, liver, and intestinal tissue, rasagiline was shown to be a potent, irreversible monooamine 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 stratum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline’s beneficial effects seen in models of dopaminergic motor dysfunction.

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

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 postdose. Multiple doses of rasagiline of 0.5, 1, and 2 mg per day resulted in complete MAO-B inhibition.

12.3 Pharmacokinetics

Rasagiline in the range of 1-6 mg demonstrated a more than proportional increase in AUC, while Cmax was dose proportional. Rasagiline mean steady-state half life is 3 hours but there is no correlation of pharmacokinetics with its pharmacological effects 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 reduced by approximately 30% and 26%, 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.
AZILECT® (rasagiline) Tablets

**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-PAl) and 3-hydroxy-1-aminoindan (3-OH-AI). In vitro experiments indicate that both routes of rasagiline metabolism are dependent on the cytochrome P450 (CYP) system, with CYP1A2 being the major isoenzyme 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 as urine and 7% of total dose in feces over a period of 38 days). Less than 1% of rasagiline was excreted as unchanged drug in urine.

**Specific Populations**

**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 Cmax 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 Cmax were increased by 7 fold and 2 fold, respectively, compared to healthy subjects [see Dosage and Administration (2.3) and Warnings and Precautions (5.5)].

**Renal Impairment**
Following repeat dose administration (8 days) of rasagiline (1 mg/day) in subjects with moderate renal impairment, rasagiline exposure (AUC) was similar to rasagiline exposure in healthy subjects, while the major metabolite 1-AI exposure (AUC) was increased by 83% and there was no change in the elimination half life for healthy 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.

**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 for healthy subjects [see Dosage and Administration (2.2) and Warnings and Precautions (5.4)].

**Theophylline**
Coadministration of rasagiline 1 mg/day and theophylline, a substrate of CYP1A2, up to 500 mg twice daily to healthy subjects (n=24) did not affect the pharmacokinetics of either drug.

**Antidepressants**
Severe CNS toxicity (occasionally fatal) associated with hyponychia as a part of serotonin syndrome, has been reported with combined treatment of an antidepressant (e.g., from one of many classes including tricyclic or tetracyclic antidepressants, SSRI, SNRI, trazolopyridine antidepressants) and nonselective MAO or a selective MAO-B inhibitor [see Warnings and Precautions (5.2)].

**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 1 mcg/mL (equivalent to a level that is 160 times the average Cmax – 5.9-8.5 ng/mL in Parkinson’s disease patients after 1 mg rasagiline 5-fold in subjects with moderate renal impairment, compared to healthy subjects. In subjects with mild hepatic impairment (Child-Pugh score 5-6), AUC and Cmax 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 Cmax were increased by 7 fold and 2 fold, respectively, compared to healthy subjects [see Dosage and Administration (2.3) and Warnings and Precautions (5.5)].

**Carcinogenesis**
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>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>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>24.7</td>
<td>0.1</td>
</tr>
<tr>
<td>AZILECT 2 mg</td>
<td>25.9</td>
<td>0.7</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 8 mg/day or pramipexole, mean 1.5 mg/day) 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>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>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>32.1</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

*A negative change from baseline indicates improvement in the UPDRS score. 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).*
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 inadequate control 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 measure 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 had a numerically smaller effect than the 1 mg dose of AZILECT. In Study 4, the active comparator also reduced “OFF” time when compared to placebo.

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

<table>
<thead>
<tr>
<th></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>

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 groups, respectively. When levodopa was reduced, it was reduced by 13% and 11% in the placebo and the AZILECT groups, respectively.

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.

Table 9: Secondary Measures of Effectiveness in Study 3

<table>
<thead>
<tr>
<th></th>
<th>Baseline (score)</th>
<th>Change from baseline to last value</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>15.5</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>AZILECT 0.5 mg</td>
<td>15.8</td>
<td>-0.60</td>
<td></td>
</tr>
<tr>
<td>AZILECT 1 mg</td>
<td>15.5</td>
<td>-0.68</td>
<td></td>
</tr>
</tbody>
</table>

In Study 4, the active comparator also reduced “OFF” time when compared to placebo. 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, 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 groups, respectively. When levodopa was reduced, it was reduced by 13% and 11% in the placebo and the AZILECT groups, respectively.

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.

Table 10: Secondary Measures of Effectiveness in Study 4

<table>
<thead>
<tr>
<th></th>
<th>Baseline (score)</th>
<th>Change from baseline to last value</th>
<th>p-value vs. placebo</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>18.7</td>
<td>-0.89</td>
<td></td>
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<tr>
<td>AZILECT 1 mg</td>
<td>19.0</td>
<td>-2.61</td>
<td></td>
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</tbody>
</table>

AZILECT® (rasagiline) 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°-30°C (59°-86°F).

16 HOW SUPPLIED/STORAGE AND HANDLING

AZILECT 0.5 mg Tablets:

ADVERSE REACTIONS

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 CYP1A2 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)].

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.

Pregnancy
Advise patients to notify their healthcare provider if they are pregnant or plan to become pregnant [see Use in Specific Populations (8.1)].