Effectiveness of Lidocaine Patch 5% in Patients With or Without Allodynia

To the Editor: ***November 9, 2006***

I would like to commend Roy Freeman, MD, on his comprehensive review on the pathophysiology and treatment of neuropathic pain.[1] He has done a fine job of condensing a complex topic into a review that is cohesive and easy to understand, and no doubt will assist clinicians in managing their patients with neuropathic pain.

I would, however, like to clarify one issue regarding the use of the lidocaine patch 5%. Freeman states that the lidocaine patch 5% "is most effective in patients with allodynia."[1] Although the original studies conducted included only patients with allodynia,[2,3] more recent clinical data suggests the lidocaine patch 5% is equally effective in patients without allodynia.

Freeman refers to an open-label study of 56 patients with painful diabetic polyneuropathy (DPN) trial by Barbano and colleagues.[4] The efficacy of the lidocaine patch 5% was specifically assessed in allodynic patients compared to those without allodynia. These groups did not differ with respect to age, gender, ethnicity, or baseline pain intensity. According to their report, the lidocaine patch 5% significantly reduced pain and improved quality of life (QOL) in all DPN patients. Furthermore, these groups (allodynia vs non-allodynia) did not differ in the magnitude of their improvement on any of the pain and QOL outcome measures, suggesting that the lidocaine patch 5% had comparable effectiveness in both groups.

Given this information, I do not believe there is sufficient evidence to conclusively state that the lidocaine patch 5% is most effective in patients with allodynia; but, rather seems to provide comparable effectiveness with or without the presence of allodynia.

Sincerely,
Arnold R. Gammaitoni, PharmD

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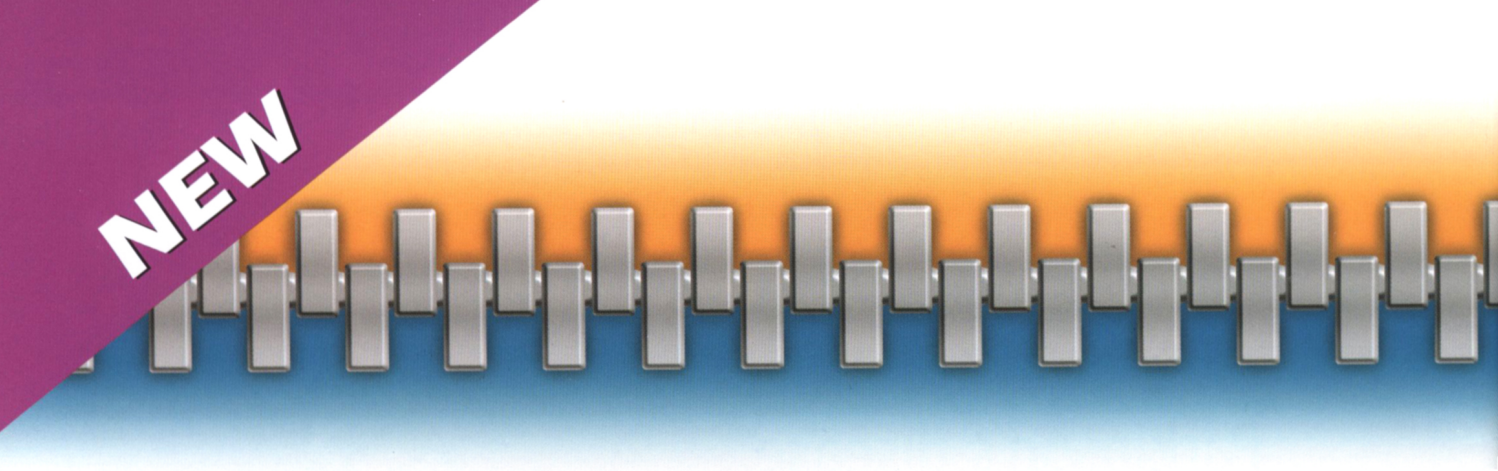
Dr. Gammaitoni is senior director of Medical Affairs for Endo Pharmaceuticals in Chadds Ford, Pennsylvania.

Disclosure: Dr. Gammaitoni receives stock-option grants as an employee of Endo Pharmaceuticals.

Please send letters to the editor to: CNS Spectrums, c/o Eric Hollander, MD, 333 Hudson St., 7th Floor, New York, NY 10013; E-mail: vj@mblcommunications.com.

https://doi.org/10.1017/S1092852900015078 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900016078 Published online by Cambridge University Press



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Important safety information.

AZILECT® (rasagiline tablets) is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD) as initial monotherapy and as adjunct therapy to levodopa. The effectiveness of AZILECT® was demonstrated in patients with early PD who were receiving AZILECT® as monotherapy and who were not receiving any concomitant dopaminergic therapy. The effectiveness of AZILECT® as adjunct therapy was demonstrated in patients with PD who were treated with levodopa.

- AZILECT® is contraindicated with meperidine. Serious reactions have been precipitated with concomitant use of meperidine and MAO inhibitors including selective MAO-B inhibitors.
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- **Patients taking AZILECT® should avoid foods and beverages high in tyramine content in order to prevent a potential hypertensive crisis. Patients should be instructed about the tyramine content of foods and beverages and amine-containing medications that should be avoided, and about the signs and symptoms of marked blood pressure elevation that could represent a hypertensive emergency requiring immediate treatment/hospitalization.**
- As with other MAOIs, patients taking AZILECT® should not undergo elective surgery requiring general anesthesia and should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors.
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- At least 14 days should elapse after discontinuation of AZILECT® before taking meperidine, antidepressants, other MAOIs, exogenous amines, or general anesthesia for elective surgery, or resuming an unrestricted diet.
- Caution should be used when giving AZILECT® concurrently with CYP1A2 inhibitors such as ciprofloxacin.
- Patients with moderate to severe hepatic impairment or pheochromocytoma should not take AZILECT®.
- An increased incidence of melanoma in the AZILECT® development program was comparable to that observed in the PD populations examined in epidemiological studies. PD patients are advised to monitor for melanoma frequently and see a dermatologist on a regular basis.

Side effects as monotherapy (AZILECT® 1 mg vs placebo, respectively) include: headache (14% vs 12%), arthralgia (7% vs 4%), and dyspepsia (7% vs 4%); and as adjunct to levodopa therapy (AZILECT® 1 mg, 0.5 mg, and placebo, respectively) include: dyskinesia (18%, 18%, 10%), accidental injury (12%, 8%, 5%), nausea (12%, 10%, 8%), weight loss (9%, 2%, 3%), constipation (9%, 4%, 5%), postural hypotension (9%, 6%, 3%), arthralgia (8%, 6%, 4%), vomiting (7%, 4%, 1%), dry mouth (6%, 2%, 3%), rash (6%, 3%, 3%), and somnolence (6%, 4%, 4%).

Please see brief summary of prescribing information on the following pages.

References: **1.** The Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease. The TEMPO study. *Arch Neurol.* 2002;59:1937-1943. **2.** Data on file, Teva Neuroscience, Inc. **3.** AZILECT® Prescribing Information. **4.** The Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations. The PRESTO study. *Arch Neurol.* 2005;62:241-248. **5.** Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet.* 2005;365(9463):947-954.

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AZILECT® (rasagiline tablets), 0.5 and 1 mg

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

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

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

Sympathomimetic Amines: Like other MAOIs, AZILECT is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). Severe hypertensive reactions have followed the administrations of sympathomimetics and non-selective MAO inhibitors. At least one case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine).

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

Surgery: As with other MAOIs, patients taking AZILECT should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. AZILECT should be discontinued at least 14 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

Pheochromocytoma: As with other MAOIs, AZILECT is contraindicated in patients with pheochromocytoma.

WARNINGS

Need for Restriction of Dietary Tyramine and Amines Contained in Medications

AZILECT treatment at any dose may be associated with a hypertensive crisis/"cheese reaction" if the patient ingests tyramine-rich foods, beverages, or dietary supplements or amines (from over-the-counter medications). Hypertensive crisis, which in some cases may be fatal, consists of marked systemic blood pressure elevation and requires immediate treatment/hospitalization.

MAO in the gastrointestinal tract and liver (primarily type A) is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a hypertensive crisis, the so-called "cheese reaction." If significant amounts of certain exogenous amines gain access to the systemic circulation – e.g., tyramine from fermented cheese, red wine, herring, or amines contained in over-the-counter cough/cold medications – they can cause release of norepinephrine, which may significantly increase systemic blood pressure. MAO inhibitors that selectively inhibit MAO-B are generally devoid of the potential to cause a hypertensive crisis/"cheese reaction" at defined relatively low doses at which tyramine sensitivity has been characterized. The selectivity of rasagiline for inhibiting MAO-B (and not MAO-A) in humans has not been sufficiently characterized to permit rasagiline treatment without restriction of dietary tyramine or amines contained in medications. Even for "selective" MAO-B inhibitors, the selectivity for inhibiting MAO-B typically diminishes and is ultimately lost as the dose is increased beyond particular dose levels.

Patients receiving rasagiline should be instructed about the tyramine content of foods and beverages (see table below) and amine containing medications that should be avoided. Sympathomimetic amines found in over-the-counter medicines to be avoided include pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine.

It is also necessary to maintain this dietary tyramine restriction and avoidance of exogenous amines contained in medications for 2 weeks following discontinuation of rasagiline because of the irreversible inhibition of the MAO enzyme and the need for new MAO enzyme synthesis.

Patients should also be instructed about the signs and symptoms of marked blood pressure elevation that could represent a hypertensive emergency requiring immediate treatment/hospitalization. These include severe headache, blurred vision/visual disturbances, difficulty thinking, stupor/coma, seizures, chest pain, unexplained nausea or vomiting, or signs or symptoms of a stroke.

Patients should be told to immediately contact a medical provider to report any severe headache or other atypical or unusual symptoms not previously experienced that could be due to a hypertensive crisis. (See PRECAUTIONS-Information for Patients, OVERDOSE, DOSAGE AND ADMINISTRATION).

Class of Food or Beverage	Tyramine-rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation, red wines	Bottled and canned beers and white wines contain little or no tyramine
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

Adapted from K. I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384

Coadministration with Antidepressants

Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combination of tricyclic antidepressants and non-selective MAOIs (e.g., Nardil, Parnate) or a selective MAO-B inhibitor, selegiline (Eldepryl). These adverse events have included behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, syncope and death.

Serious, sometimes fatal, reactions with signs and symptoms including hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma have been reported in patients receiving a combination of selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (Prozac), fluvoxamine (Luvox), sertraline (Zoloft), and paroxetine (Paxil) and non-selective MAOIs or the selective MAO-B inhibitor selegiline. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or the selective MAO-B inhibitor selegiline.

AZILECT clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with AZILECT, but the following antidepressants and doses were allowed in the AZILECT trials: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily and paroxetine ≤ 30 mg/daily.

Although a small number of rasagiline-treated patients were concomitantly exposed to antidepressants (tricyclics n=115; SSRIs n=141), the exposure, both in dose and number of subjects, was not adequate to rule out the possibility of an untoward reaction from combining these agents. Furthermore, because the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid the combination of AZILECT with tricyclic, SSRI, or SNRI (serotonin-norepinephrine reuptake inhibitor) antidepressants. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with a tricyclic, SSRI, or SNRI antidepressant. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of AZILECT. (See **PRECAUTIONS, Drug Interactions**, *Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic and Tetracyclic Antidepressants).*

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

Hepatic Insufficiency: Rasagiline plasma concentration may increase in patients with mild (up to 2 fold, Child-Pugh score 5-6), moderate (up to 7 fold, Child-Pugh score 7-9), and severe (Child-Pugh score 10-15) hepatic impairment. Patients with mild hepatic impairment should be given the dose of 0.5 mg/day. AZILECT should not be used in patients with moderate or severe hepatic impairment. (See **CLINICAL PHARMACOLOGY, Special Populations**).

PRECAUTIONS

General

Melanoma: Comparison of the rates of melanoma in the AZILECT development program with rates in age- and sex-matched populations from two epidemiologic data bases (Surveillance, Epidemiology, and End Results Registry of the National Cancer Institute and the American Academy of Dermatology Skin Cancer Screening Program) showed a risk of melanoma that was greater in patients treated with rasagiline than in the general population. Some epidemiological studies, however, have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population, although it was unclear whether the observed increased risk was due to Parkinson's disease itself or to drugs used to treat Parkinson's disease. The increased incidence of melanoma in the AZILECT development program was comparable to the increased risk observed in the Parkinson's disease populations examined in these epidemiological studies.

For the reasons stated above, patients and providers 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).

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

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

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

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

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

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

Patients should be cautioned of the possibility of developing hallucinations and instructed to report them to their health care provider promptly should they develop.

Information for Patients

Patients and caregivers should be informed about which foods and beverages to avoid because of high tyramine content. They should be informed that a hypertensive crisis could occur after ingestion of certain foods (e.g., aged cheeses, pickled herring, yeast extract) or beverages (e.g., some red wines and certain beers) containing significant amounts of tyramine, or amines contained in some medications including some over-the-counter cough/cold medications. Foods high in tyramine content include those that have undergone protein change by aging, fermentation, pickling, or smoking to improve flavor such as aged cheeses, air-dried meats, sauerkraut, soy sauce, tap/draft beers and red wines. The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

Patients and caregivers should be informed of the signs and symptoms associated with hypertensive crisis, including severe headache, blurred vision, difficulty thinking, seizures, chest pain, unexplained nausea or vomiting, or signs or symptoms of a stroke. Patients and caregivers should seek immediate medical attention for patients who develop any severe headache or other atypical or unusual symptoms not previously experienced. (See **WARNINGS**).

Patients should 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. Patients should not use meperidine with AZILECT.

Patients taking AZILECT as adjunct to levodopa should be advised there is the possibility of increased dyskinesia and postural hypotension.

Patients 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).

Patients should be instructed 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.

Drug Interactions

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

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

Sympathomimetic Medications: The concomitant use of AZILECT and sympathomimetic medications was not allowed in clinical studies. Severe hypertensive reactions have followed the administration of sympathomimetics and non-selective MAO inhibitors. One case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine). Therefore, in view of AZILECT's MAO inhibitory activity, AZILECT should not be used concomitantly with sympathomimetics including nasal and oral decongestants and cold remedies. (See **CONTRAINDICATIONS** and **WARNINGS**, ***Need for Restriction of Dietary Tyramine and Amines Contained in Medications***).

MAO Inhibitors: AZILECT should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. (See **CONTRAINDICATIONS**).

Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic and Tetracyclic Antidepressants: Concomitant use of SSRI, tricyclic, and tetracyclic antidepressants with AZILECT is not recommended. (See **WARNINGS**).

Levodopa/carbidopa: (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions; PRECAUTIONS, General,** *Dyskinesias Due to Levodopa Treatment*).

Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations may increase up to 2 fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. This could result in increased adverse events. (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** and **WARNINGS**, *Ciprofloxacin and Other CYP1A2 Inhibitors*).

Theophylline: (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

Laboratory Tests

No specific laboratory tests are required for the treatment of patients on AZILECT.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Rasagiline was also negative in the *in vivo* micronucleus assay in CD-1 mice when administered in combination with levodopa/carbidopa.

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

Pregnancy Category C

No effect on embryo-fetal development was observed in a combined mating/fertility and embryo-fetal development study in female rats at doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [MRHD, 1 mg/day]). Effects on embryo-fetal development in rabbit have not been adequately assessed.

In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) orally, from the beginning of organogenesis to day 20 post-partum, offspring survival was decreased and offspring body weight was reduced at doses of 0.3 mg/kg/day and 1 mg/kg/day (10 and 16 times the expected plasma rasagiline exposure [AUC] at the MRHD). No plasma data were available at the no-effect dose (0.1 mg/kg); however, that dose is 1 times the MRHD on a mg/m^2 basis. Rasagiline's effect on physical and behavioral development was not adequately assessed in this study.

Rasagiline may be given as an adjunct therapy to levodopa/carbidopa treatment. In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day) (alone and in combination) throughout the period of organogenesis, there was an increased incidence of wavy ribs in fetuses from rats treated with rasagiline in combination with levodopa/carbidopa at 1/80/20 mg/kg/day (approximately 8 times the plasma AUC expected in humans at the MRHD and 1/1 times the MRHD of levodopa/carbidopa [800/200 mg/day] on a mg/m^2 basis). In a study in which pregnant rabbits were dosed throughout the period of organogenesis with rasagiline alone (3 mg/kg) or in combination with levodopa/carbidopa (rasagiline: 0.1, 0.6, 1.2 mg/kg, levodopa/carbidopa: 80/20 mg/kg/day), an increase in embryo-fetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day when administered in combination with levodopa/carbidopa (approximately 7 and 13 times, respectively, the plasma rasagiline AUC at the MRHD). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone (1/1 times the MRHD on a mg/m^2 basis) and to a greater extent when rasagiline (at all doses; 1-13 times the plasma rasagiline AUC at the MRHD) was administered in combination with levodopa/carbidopa.

There are no adequate and well-controlled studies of rasagiline in pregnant women. Therefore, AZILECT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In rats rasagiline was shown to inhibit prolactin secretion and it may inhibit milk secretion in females.

It is not known whether rasagiline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AZILECT is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of AZILECT in the pediatric population have not been studied.

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 non-geriatric patients.

ADVERSE REACTIONS

During the clinical development of AZILECT, 1361 Parkinson's disease patients received rasagiline as initial monotherapy or as adjunct therapy to levodopa. As these two populations differ, not only in the adjunct use of levodopa during rasagiline treatment, but also in the severity and duration of their disease, they may have differential risks for various adverse events. Therefore, most of the adverse events data in this section are presented separately for each population.

Patients receiving AZILECT as initial monotherapy treatment

Adverse Events Leading to Discontinuation in Controlled Clinical Studies:

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

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

Adverse Event Incidence in Controlled Clinical Studies:

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

Table 6 lists treatment-emergent adverse events that occurred in ≥ 2% of patients receiving AZILECT as monotherapy participating in the double-blind, placebo-controlled trial and were numerically more frequent than in the placebo group.

Table 6. Treatment-Emergent* Adverse Events in AZILECT 1 mg-Treated Monotherapy Patients

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

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

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

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

Patients receiving AZILECT as adjunct to levodopa therapy

Adverse Events Leading to Discontinuation in Controlled Clinical Studies:

In a double-blind, placebo-controlled trial (Study 1) conducted in patients treated with AZILECT as adjunct to levodopa therapy, approximately 9% of the 164 patients treated with AZILECT 0.5 mg/day and 7% of the 149 patients treated with AZILECT 1 mg/day discontinued treatment due to adverse events compared to 6% of the 159 patients who received placebo. The AEs that led to discontinuation of more than one rasagiline-treated patient were: diarrhea, weight loss, hallucination, and rash. Adverse event reporting was considered more reliable for Study 1 than for the second controlled trial (Study 2); therefore only the adverse event data from Study 1 are presented in this section of labeling.

Adverse Event Incidence in Controlled Clinical Studies:

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

Table 7 lists treatment-emergent adverse events that occurred in ≥ 2% of patients treated with AZILECT 1 mg/day as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (Study 1) and that were numerically more frequent than the placebo group. The table also shows the rates for the 0.5 mg group in Study 1.

Table 7. Incidence of Treatment-Emergent* Adverse Events in Patients Receiving AZILECT as Adjunct to Levodopa Therapy in Study 1

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

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

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

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

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

Other Adverse Events Observed During All Phase 2/3 Clinical Trials

Rasagiline was administered to approximately 1361 patients during all PD phase 2/3 clinical trials. About 283 patients received rasagiline for at least one year, approximately 410 patients received rasagiline for at least two years, 116 patients received rasagiline for at least 3 years, and 245 patients received rasagiline for more than 3 years, with some patients treated for more than 5 years. The long-term safety profile was similar to that observed with shorter duration exposure.

The frequencies listed below represent the proportion of the 1361 individuals exposed to rasagiline who experienced events of the type cited.

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

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

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

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

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

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

Metabolic and Nutritional disorders: *Infrequent:* hypocalcemia

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

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

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

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

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

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

OVERDOSE

No cases of AZILECT overdose were reported in clinical trials.

Rasagiline was well tolerated in a single-dose study in healthy volunteers receiving 20 mg/day and in a ten-day study in healthy volunteers receiving 10 mg/day. Adverse events were mild or moderate. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg of rasagiline there were three reports of cardiovascular side effects (including hypertension and postural hypotension) which resolved following treatment discontinuation.

Symptoms of overdosage, although not observed with rasagiline during clinical development, may resemble those observed with non-selective MAO inhibitors.

Although no cases of overdose have been observed with rasagiline, the following description of presenting symptoms and clinical course is based upon overdose descriptions of non-selective MAO inhibitors.

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

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

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

There is no specific antidote for rasagiline overdose. The following suggestions are offered based upon the assumption that rasagiline overdose may be modeled after non-selective MAO inhibitor poisoning. Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

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

Rx only

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Teva Pharmaceutical Industries Ltd.
Kfar Saba 44102, Israel
Marketed by:
Teva Neuroscience, Inc.
Kansas City, MO 64131