

# drug information perspectives

Volume 28 (3) 2008

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**Chairman, Medical Review**

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## RASAGILINE

**TRADE NAME:** Azilect

**SYNONYM:** TVP-1012; R-isomer of AGN 1135

**CLASSIFICATION:**

- Antiparkinson
- Monoamine oxidase inhibitor
- Propargylamine

**ACTION:**

- Irreversible monoamine oxidase (MAO) inhibitor.
- By inhibiting MAO-B, it reduces the degradation of endogenous and exogenous dopamine in the brain, increasing dopamine levels. MAO-B is completely inhibited by multiple doses of 0.5mg/day.
- MAO-A makes up 80% of the MAO in the intestines, 50% of MAO in the liver, and 25% of MAO in the brain, and preferentially metabolizes norepinephrine, epinephrine, and serotonin, as well as metabolizing dopamine and dietary tyramine. MAO-B is the main form in the brain (75% of brain MAO), and makes up 50% of liver MAO and 20% of intestinal MAO; MAO-B preferentially metabolizes phenylethylamine and benzylamine and also metabolizes tyramine and dopamine.
- More selective for MAO-B than MAO-A in animals, by a factor of 17-100. In a study of intestinal MAO in rats, rasagiline produced 61% inhibition of MAO-A and 80% inhibition of MAO-B; selectivity depended on dose, and the relationship of this dose to a therapeutic dose in humans is unclear. Selectivity for MAO-B versus MAO-A is not established in humans. In a study of human brain homogenates, the IC<sub>50</sub> levels for inhibition of MAO-A and MAO-B were 7.1x10<sup>-7</sup> and 1.4x10<sup>-8</sup> M, respectively, a 51-fold difference.
- No intrinsic sympathomimetic activity.

**PHARMACOKINETICS:**

**Half-life:**

- 3 hours (but effect lasts longer because MAO-B is irreversibly inhibited)

**Absorption:**

- Quickly absorbed. Oral bioavailability 36%. Administration with food reduces C<sub>max</sub> 60% but reduces AUC only 20%. T<sub>max</sub> 0.5-0.7 hours after a dose.

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**Distribution:**

- Highly plasma protein bound (90%).

**Metabolism:**

- Almost completely metabolized, mainly by CYP 1A2. Major metabolite 1(R)-aminoindan is a weak, nonselective, reversible inhibitor of MAO.

**Elimination:**

- Eliminated as metabolites, mainly by renal excretion (62% of dose) plus some fecal excretion (7%).

**Special populations:**

- **Elderly:** No relevant difference.
- **Children under 18 years:** No data.
- **Hepatic impairment:** Mild hepatic impairment (Child-Pugh score 5-6): AUC increases 2-fold. Moderate hepatic impairment (Child-Pugh score 7-9): AUC increases 7-fold.
- **Renal impairment:** No data.
- **Gender:** No relevant difference.
- **Race:** No data.

**USES AND EFFICACY:****Uses:**

- Treatment of the symptoms of **Parkinson's Disease**, either as initial monotherapy in early disease or in combination with levodopa. As **early therapy** in patients not requiring dopaminergic drugs, it improves motor symptoms, activities of daily living (ADL), and quality of life (QOL). As an **adjunct to reduce motor fluctuations** in patients receiving levodopa, it reduces off-time up to 14%, increases on-time without dyskinesias, and improves ADL, motor performance, freezing, postural instability and gait, and early morning akinesia.

**Clinical course:**

- MAO-B is irreversibly inhibited for at least 1 week after the last dose. Reduction in off-time is seen within 6 weeks of starting therapy. Benefit is still detectable 6 weeks after discontinuation.

**Major clinical trials**

**TEMPO study (2002):** Four hundred and four patients with early Parkinson's disease who were not receiving dopaminergic drugs (initial Unified Parkinson's Disease Rating Scale (UPDRS) approximately 25) were randomized to receive rasagiline 1mg/day, rasagiline 2mg/day or placebo in a double-blind fashion. Excluded patients were those with dementia, depression, heart failure or unstable medical problems. After 6 months, patients given the approved dose of 1mg/day had significantly better UPDRS scores by an average of 4.2 units (score range 0-180), due to better scores on ADL and motor symptoms, compared with placebo. Patients given 1mg/day or 2mg/day had a similar percentage of responders (66-67%), defined as less than a 3 unit worsening of the UPDRS score, compared with a 49% response rate in the placebo group. QOL was significantly better with rasagiline treatment. There was no difference in the percentage of patients who needed dopaminergic therapy. No statistically significant benefit was found on cognition, rigidity, bradykinesia, or depression.

**Extension of TEMPO study (2004):** In a continuation of the TEMPO study above, patients who had been given placebo for the first six months were then given rasagiline 2mg/day (delayed treatment group), while the initial 2mg/day group continued to receive the same dose (early treatment group). After 52 weeks, the early treatment group had a significantly better UPDRS score than the delayed treatment group by 2.29 units. One interpretation of this result is that rasagiline slows the progression of Parkinson's disease, and does not just relieve symptoms. In an open-label extension to an average of 5.4 years of rasagiline 1mg/day, the early treatment group maintained a statistically significant benefit over the delayed treatment group. Study limitations: More proof is needed before it can be concluded that rasagiline is disease-modifying. The analysis included patients who required and began to receive dopaminergic drugs during the study, which may have biased the results. When only the patients who did not receive added dopaminergic therapy are evaluated, the difference between early and delayed treatment is not statistically significant. In a separate analysis the QOL after 52 weeks did not differ between early and delayed therapy. Delayed dosing with the approved dose of 1mg/day was not tested.

**PRESTO study (2006):** Patients with advanced Parkinson's disease (n=472) who had developed motor fluctuations (average 6hours/day off-time, 1hour/day on-time with dyskinesias) while taking levodopa (average 8years) were given rasagiline 0.5mg/day, rasagiline 1mg/day or placebo in a randomized, double-blind study. Levodopa dose adjustments were restricted. After 26 weeks, off-time was significantly reduced by 8% (0.49 hours) in the group given rasagiline 0.5mg/day, and by 14% (0.94 hours) when given rasagiline 1mg/day, versus placebo. A dose of 1mg/day increased on-time without dyskinesias, improved ADL, tremor, rigidity, bradykinesia and motor function, compared with placebo. The lower dose improved ADL, motor performance, tremor, postural instability and gait. Quality of life was unchanged. Dyskinesias increased at the 1mg dose, which might have been avoided by lowering the levodopa dose.

### **Comparisons**

#### **Vs. entacapone**

- Rasagiline and entacapone produce similar reductions in off-time in patients with motor fluctuations receiving levodopa.

#### **Vs. other antiparkinson agents**

- Direct comparisons are not available. Other drugs may be equally or more effective in reducing off-time in patients with motor fluctuations receiving levodopa. Selegiline may be neuroprotective, but this remains controversial.

#### **Advantages:**

- Well tolerated, with infrequent sleep disorders or hallucinations, and no reduction in cognition.
- Unlike selegiline, it is not metabolized to amphetamine derivatives with sympathomimetic activity.
- Once daily dosing without regard for meals.
- Long-term efficacy and safety for up to 6 years as monotherapy.

#### **Disadvantages:**

- Appears less effective at symptom control than dopamine agonists or levodopa.
- Controversy exists over whether or not there is a need to restrict tyramine in the diet (see Place in Therapy).
- Many contraindications and serious drug interactions.

#### **Place in therapy:**

- **Initial therapy of Parkinson's Disease:** Modest benefit is achieved (better by 4 units on UPDRS compared with placebo after 6 months). Levodopa is the most effective drug for symptom control but long-term administration is associated with motor complications (motor fluctuations and dyskinesias). Dopamine agonists are used as alternative initial therapy, especially in younger patients, to postpone treatment with levodopa and the common motor complications. Rasagiline monotherapy is an alternative to dopamine agonists that also allows patients to postpone treatment with levodopa, with few side effects, although it may pose a risk of tyramine-related reactions. It is considered to be less effective at symptom control than levodopa. Consider individual patient factors including life expectancy, severity of symptoms and possible drug interactions. Levodopa may be a better choice in elderly patients who could benefit from the greater symptom control, perhaps enabling them to continue independent living.
- **Adjunct to levodopa in patients with motor fluctuations:** Produces mild to moderate reduction in off-time in patients with moderate to severe Parkinson's Disease. Rasagiline is one of many possible adjuncts to levodopa, with no proven superiority over other drugs.
- **Disease modification** due to neuroprotection and/or neurorescue has been postulated. There is considerable evidence in animal and cell models that this drug reduces neuronal damage following physical or toxin-related trauma. In humans, earlier treatment may produce slightly better outcomes (2 units on the 180 unit UPDRS) than treatment delayed by 6 months, but further study is required to distinguish neuroprotection from symptomatic effects of the drug. No drugs have been proven to be disease-modifying in Parkinson's disease.
- **No evidence** that it prevents motor complications associated with levodopa. However, since these are believed to be related to nonphysiologic pulsatile dopamine receptor stimulation, the irreversible MAO inhibition may produce more consistent dopamine levels.
- **No evidence** that it helps nonmotor symptoms of Parkinson's Disease (fatigue, pain, sleep disorders, reduced cognition).

## CONTRAINDICATIONS AND PRECAUTIONS:

### Contraindications:

- **Hypersensitivity**
- **Dextromethorphan** (possible psychosis, bizarre behaviour, serotonin syndrome)
- **Meperidine, methadone, propoxyphene, tramadol** (severe hypertension, respiratory depression, CNS depression, malignant hyperthermia, seizures, and death have occurred when combined with MAO inhibitors).
- **St. John's wort, mirtazapine, cyclobenzaprine** (possible serotonin syndrome)
- **Sympathomimetic amines** (amphetamines, phenylephrine, ephedrine, pseudoephedrine, phenylpropanolamine; possible hypertensive crisis)
- **MAO inhibitors** (hypertensive crisis; allow 14 days between therapy)
- **General anesthetics, cocaine, local anesthetics containing vasoconstrictors** (discontinue at least 14 days prior to surgery)
- **Antidepressants, including SSRIs, SNRIs, tricyclic antidepressants, tetracyclic antidepressants** (hypertension, death, serotonin syndrome; allow at least 14 days in between therapy, and at least 5 weeks for fluoxetine)
- **Moderate or severe renal impairment** (no data)
- **Moderate or severe liver impairment** (increased serum levels)
- **Pheochromocytoma**

### Precautions:

- **Tyramine-rich foods and diet restriction:** Controversy exists over whether or not there is a need to restrict tyramine in the diet during rasagiline therapy. Tyramine-rich foods can lead to hypertensive crisis by causing norepinephrine release. MAO-A in the GI tract usually protects against this effect by metabolizing tyramine. In Canada, dietary restriction is not recommended if no more than 1mg/day of rasagiline is ingested. However, since the selectivity of rasagiline for MAO-B versus MAO-A is not well established in humans, and low doses have been associated with increased blood pressure following a tyramine challenge, it would be prudent to inform the patient and caregiver of possible precautions and warning signs. Diet restriction is recommended in the United States. US guidelines recommend avoidance of tyramine-containing food during therapy and for two weeks following discontinuation. Teach patients the foods that contain tyramine and the symptoms of hypertensive crisis (see PATIENT INSTRUCTIONS).
- **Elderly** patients (when combined with levodopa, increased risk of hallucinations; possible increased risk of orthostatic hypotension).
- **Melanoma** (increased risk in patients with Parkinson's Disease, possibly increased by rasagiline; monitor)
- **Smoking** (possible decreased rasagiline levels because smoking induces CYP1A2 and rasagiline is primarily metabolized by CYP1A2).
- **Report** unexpected or serious reactions to the Canada Vigilance Program.

## PREGNANCY AND LACTATION:

- No toxicity detected in animal studies. No human data; consider risk:benefit. Inhibits prolactin secretion, and thus may inhibit lactation. Caution while breast-feeding.

## SIDE EFFECTS:

Generally well tolerated. Dopaminergic side effects (nausea, vomiting, postural hypotension, hallucinations, dyskinesias) occur when combined with levodopa, as predicted by the mechanism of action of rasagiline, and may be alleviated by reducing the levodopa dose.

**Cardiovascular:** Postural hypotension (when combined with levodopa, 6-9% versus placebo 3%; mostly in the first two months); bundle branch block (at least 1%). Blood pressure is not increased at recommended doses.

**CNS:** Headache (14% versus placebo 10%); depression (5% versus placebo 2%); sleep disturbance/insomnia (when combined with levodopa, 8% versus placebo 6%); hallucinations (when combined with levodopa, 1.3% vs. placebo 0.7%, up to 5%, may be severe. Increased risk in elderly over age 70 (12% versus placebo 2%)); asthenia (at least 1%). Cognition is not adversely affected.

**Gastrointestinal:** Nausea (when combined with levodopa, 10-12% versus placebo 8%); vomiting (when combined with levodopa, 7% versus placebo 1%); dry mouth (when combined with levodopa, up to 6% versus placebo 3%); anorexia (when combined with levodopa, 5.4% versus placebo 0.6%); GI hemorrhage (at least 1%).

**Genitourinary:** Hematuria, urinary incontinence (at least 1%).

**Musculoskeletal:** Dyskinesias (when combined with levodopa, 18% versus placebo 10%); arthralgia (7% versus placebo 4%); hyperkinesia, tremor (at least 1%).

**Neurologic:** Abnormal gait (at least 1%).

**Respiratory:** Flu syndrome (5% versus placebo 1%); increased cough (at least 1%).

**Other:** Falls (5% versus placebo 3%); balance difficulty (3-5% versus placebo 0.6%); accidental injury (when combined with levodopa, 8-12% versus placebo 5%); weight loss (when combined with levodopa, up to 9% versus placebo 3%); malignant melanoma (case reports; patients with Parkinson's disease are at increased risk of melanomas and the influence of drug therapy is not clear).

**INTERACTIONS:**

Does not inhibit P450 enzymes.

<b>DRUG</b>	<b>EFFECT</b>	<b>MECHANISM</b>	<b>IMPORTANCE</b>
Anesthetics, general*	Severe serotonin syndrome-like reaction	Unknown	Contraindicated, discontinue 14 days before surgery
Antidepressants* (SSRIs, SNRIs, TCAs, mirtazapine)	Serotonin syndrome	Decreased serotonin metabolism by MAO-A; serotonin increase by antidepressant	Contraindicated, allow 14 days in between, at least 5 weeks for fluoxetine
Cyclobenzaprine*	Serotonin syndrome	Decreased serotonin metabolism by MAO-A; possibly serotonergic	Contraindicated, allow 14 days in between
Dextromethorphan*	Serotonin syndrome	Decreased serotonin metabolism by MAO-A; possibly serotonergic	Contraindicated, allow 14 days in between
Drugs that inhibit CYP 1A2**	Increased rasagiline levels	Decreased metabolism	Maximum 0.5 mg/day; monitor
Drugs that induce CYP 1A2***	Decreased rasagiline levels	Increased metabolism	Caution
Levodopa	Increased rasagiline levels; increased dopaminergic side effects; worsened dyskinesias; hypotension	Excessive increase in dopamine levels	Reduce levodopa dose
MAOIs (all)	Additive toxicity	Additive	Contraindicated, allow 14 days in between

Meperidine*	Increased CNS and cardio-respiratory depression; paradoxical CNS and sympathetic stimulation	Unknown, possibly serotonergic	Contraindicated, allow 14 days in between
Methadone*	Increased CNS and cardio-respiratory depression; paradoxical CNS and sympathetic stimulation	Unknown, possibly serotonergic	Contraindicated, allow 14 days in between
Propoxyphene*	Increased CNS and cardio-respiratory depression; paradoxical CNS and sympathetic stimulation	Unknown, possibly serotonergic	Contraindicated, allow 14 days in between
St. John's wort*	Serotonin syndrome	Decreased serotonin metabolism by MAO-A; serotonin increase by herbal	Contraindicated, allow 14 days in between
Sympathomimetics, indirect* (ephedrine, pseudoephedrine, phenylephrine, phenylpropanolamine, cocaine, amphetamines, methylphenidate)	Hypertensive crisis	Decreased MAO-A metabolism increases norepinephrine available for release by indirect sympathomimetics	Contraindicated, allow 14 days in between
Tramadol*	Increased CNS and cardio-respiratory depression; paradoxical CNS and sympathetic stimulation	Unknown, possibly serotonergic	Contraindicated, allow 14 days in between

\* Some interactions (marked with \*) are potentially severe, although theoretical and based on unclear mechanisms including the possibility that rasagiline is not always selective for MAO-B and might inhibit MAO-A. Because of the potential severity, these interaction warnings should be followed.

\*\* **Drugs that inhibit CYP 1A2 include:** Cimetidine, ciprofloxacin, clarithromycin, erythromycin, estrogen, fluvoxamine, gemfibrozil, isoniazid, ketoconazole, norfloxacin.

\*\*\* **Drugs that induce CYP 1A2 include:** Omeprazole.

**Interactions lacking**

A lack of pharmacokinetic interaction has been documented with  
- Theophylline

**DOSAGE:****Guidelines**

- Although higher doses were used in initial clinical trials, the safety of doses above 1mg/day is not established, especially with respect to selectivity for MAO-B.

**Adults:**

- Parkinson's disease: Monotherapy: 1mg once daily. Adjunctive therapy with levodopa: Initially 0.5mg once daily. May be increased to 1mg once daily. Consider reducing the dose of levodopa if dopaminergic side effects (dyskinesias, hallucinations) occur.  
- Maximum dose 1mg once daily.

**Ciprofloxacin or other CYP 1A2 inhibitors concomitantly:** 0.5mg once daily.

**Elderly:**

- No dosage adjustment.

**Hepatic impairment:**

- Mild liver impairment (Child-Pugh score 5-6): 0.5mg once daily. Not recommended in patients with moderate or severe liver impairment.

**Renal impairment:**

- Mild renal impairment: No dosage adjustment. Moderate-severe renal impairment: Not recommended due to lack of data.

**NURSING IMPLICATIONS:**

May be administered with or without food.

Severe hypertensive crisis can occur if combined with certain drugs or foods. The symptoms of hypertensive crisis include: unexplained nausea or vomiting, severe headache, altered vision, chest pain, difficulty thinking or stupor, seizures, or the symptoms of a stroke. If these symptoms occur, obtain immediate medical aid.

Monitor for improvements in Parkinson's disease: Increased ability to perform activities of daily living, improved walking, increased ability to move.

**PATIENT INSTRUCTIONS:**

Rasagiline (ra-SA-ji-leen) is used for the treatment of Parkinson's disease.

This drug may be administered with or without food. It is usually taken once a day. Taking it at the same time each day will make it easier to remember.

Do not exceed the maximum dose. Doing so can lead to severe increase in BP. Symptoms include unexplained nausea or vomiting, severe headache, altered vision, chest pain, difficulty thinking or stupor, seizures, or the symptoms of a stroke. If these symptoms occur, obtain immediate medical aid.

If a dose is missed, take the next dose at the usual time the next day. Don't take a double dose to make up for a missed dose.

Interactions are possible, even with over-the-counter drugs. Don't take any medications, even herbal products, over-the-counter drugs, cough and cold preparations, or weight loss pills, without checking first with your physician or pharmacist. Because of the possibility of adverse drug interactions, it is important that you tell all health care professionals that you are taking this medication. A Medic Alert bracelet may be useful.

Your physician may recommend that you avoid certain foods while taking this drug. High doses of this drug may cause an undesirable increase in blood pressure with certain foods that contain tyramine. If you are taking high doses or are told to watch your diet, avoid these foods: aged cheese; pickled fish including pickled herring; liver; yeast extract such as Marmite; aged and fermented meat such as salami and some sausages; extracts such as Bovril, Oxo; soybean products including tofu and soy sauce; broad bean pods/fava bean pods; red wine, tap beer and unpasteurized beer. Safe foods include luncheon meats, hot dogs and breakfast sausage; yoghurt; processed cheese; mozzarella, ricotta, and cottage cheese; soy milk; bottled and canned beer; white wine. If the symptoms of very high blood pressure occur (unexplained nausea or vomiting, severe headache, altered vision, chest pain, difficulty thinking or stupor, seizures, or the symptoms of a stroke), go to the nearest hospital emergency department immediately.

When you first start taking this drug with levodopa, dyskinesias and postural hypotension may be more common. Inform your physician immediately if this occurs since the dose of levodopa may need adjustment.

Report any unusual reactions, such as hallucinations, to your physician.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

**PRESENTATION:**

Tablets: 0.5, 1mg.

References are available on request.

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