

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Rasagiline

Product: RASAGILINE (Azilect®)
0.5mg and 1mg tablet

Class of drugs:
Monoamine oxidase inhibitor—Type B

Indication:
Treatment of Parkinson's disease

Manufacturer: Teva Neuroscience

CED Recommendation-

The CED recommended that rasagiline (Azilect®) not be listed on the ODB Formulary but be funded via the Exceptional Access Program according to specific criteria, on the basis that rasagiline may be a reasonable option for patients who have failed formulary alternatives.

Executive Officer Decision

Based on the CED's recommendation and a subsequent listing agreement with the manufacturer that addresses cost, the Executive Officer decided to fund rasagiline (Azilect®) through the Exceptional Access Program.

Status

Funding available through the Ontario Public Drug Programs under the EAP, according to specific criteria.

Highlights of Recommendation:

- ◆ Rasagiline is used for the treatment of Parkinson's disease, either as a single agent or in combination with levodopa.
- ◆ When compared to placebo, rasagiline was shown to improve several measures of motor control and involuntary movements. In comparison to entacapone, rasagiline was comparable in efficacy and safety.
- ◆ There are no studies comparing rasagiline to selegiline, the most relevant comparator. Rasagiline and selegiline belong to the same class of drugs but the use of selegiline has declined over the years.
- ◆ The cost of rasagiline (\$7 per day) is significantly more than selegiline (\$2 per day) or entacapone (\$6 per day) at usual doses.
- ◆ **Overall, the CED acknowledged that rasagiline was shown to provide improvements in the treatment of Parkinson's disease. However, there is no evidence that rasagiline is therapeutically superior or has better safety and tolerability than entacapone to justify the price premium. Without comparative clinical studies, it is unknown whether rasagiline offers any clinical advantage over selegiline. In consideration of the difficulty treating Parkinson's disease where there are levodopa-related on/off motor fluctuations, the CED recommended funding be considered through the EAP for selected patients.**

Background:

Parkinson's disease is a progressive, degenerative brain disorder characterized by problems with motor function, stiffness, tremor and impaired balance. Parkinson's disease occurs when dopamine-producing brain cells are depleted.

There is no cure, but medications may slow or relieve symptoms for a time. Medications can help with walking, movement and tremor. Initial response to medications can be dramatic. As Parkinson's disease progresses, medications lose their effectiveness and patients experience more side-effects from treatment, such as involuntary movements and hallucinations.

Levodopa is the most effective medication for Parkinson's disease since it is a natural substance in the body and is converted to dopamine in the brain. Levodopa is combined with carbidopa which prevents the levodopa from converting to dopamine in the blood. With time, the effect of levodopa/carbidopa becomes less stable and has an on/off effect.

Selegiline and rasagiline are monoamine oxidase B (MAO-B) inhibitors and work by blocking the actions of an enzyme that breaks down dopamine so that more dopamine is available in the brain.

Entacapone is a catechol o-methyltransferase (COMT) inhibitor which prolongs the effect of levodopa by blocking an enzyme that breaks down levodopa. Entacapone is given in combination with levodopa/carbidopa.

Pramipexole and ropinirole are dopamine agonists that mimic the effects of dopamine in the brain.

Benzotropine and trihexylphenidyl are anticholinergics used to control the tremors. Amantadine can also be used to provide short-term relief of mild symptoms of early-stage Parkinson's disease. However, the benefits of these drugs are limited by the side effects.

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Detailed Discussion:

- ◆ The CED reviewed rasagiline initially in 2007 and again in mid-2009.
- ◆ In the initial review, the CED had recommended that rasagiline not be listed on the Ontario Drug Benefit Formulary nor funded via the Exceptional Access Program on the basis that there was no direct evidence rasagiline was more effective than selegiline and the price premium cannot be justified.
- ◆ The CED considered five randomized controlled trials in its evaluation of rasagiline. All five trials were placebo controlled studies and one study included a treatment arm with entacapone.
- ◆ In patients with early Parkinson's disease who have not been previously treated with levodopa, rasagiline demonstrated statistically significant improvements in quality of life and in total score on the Unified Parkinson's Disease Rating Scale (UPDRS) compared to placebo.
- ◆ In patients who were already receiving levodopa therapy, rasagiline was associated with statistically significant improvements in motor fluctuations and incidence of dyskinesia compared to placebo. Statistically significant difference in quality of life was not demonstrated.
- ◆ There were no statistically significant differences between rasagiline and entacapone in any of the reported outcomes, including serious adverse events and adverse events.
- ◆ Both rasagiline and selegiline are MAO-B inhibitors with similar side effects including weight loss, nausea, vomiting, anorexia (appetite loss) and orthostatic hypotension (low blood pressure upon standing) and less commonly, hypertensive crisis or serotonin syndrome. In addition, MAO-B inhibitors often cannot be used at the same time with many other medications used for other diseases because of interactions. In the absence of direct comparative studies, it is unknown whether rasagiline offers any therapeutic or safety advantage over selegiline.
- ◆ The manufacturer made a resubmission outlining that entacapone is a relevant clinical comparator as entacapone is prescribed more often than selegiline. In their second review, the CED noted that the use of selegiline has declined over the years for unclear reasons and concluded that either selegiline or entacapone would be reasonable clinical comparators. However, the CED also noted that the disuse of selegiline as the

sole reason for not conducting trials using selegiline as a comparator was weak.

- ◆ At the usual doses, rasagiline costs significantly more than selegiline and entacapone. A cost-effectiveness analysis was not provided to justify the price premium.
- ◆ The manufacturer's cost analysis reported that the total costs associated with rasagiline would be similar to entacapone but this cost neutrality would not be seen for patients who are on 5 tablets of entacapone per day. In addition, based on utilization data of entacapone, there would be a significant increase in cost to the program if rasagiline was to be prescribed in place of entacapone.
- ◆ **Overall, the CED noted that there is a therapeutic gap in the treatment of advanced Parkinson's disease for patients who begin to experience the on-off motor fluctuations while on levodopa-carbidopa and who have failed selegiline or entacapone. However, based on the currently available evidence, the CED is not convinced that rasagiline should displace either selegiline or entacapone. As such, the CED recommended that rasagiline be funded through the Exceptional Access Program according to clinical criteria.**

EAP Criteria:

Funding for rasagiline is provided through the Exceptional Access Program according to the following criteria:

For the treatment of Parkinson's disease

- ◆ *With 25% of the waking day in the off-state despite maximum tolerated doses of levodopa AND*
- ◆ *After failure of selegiline.*

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that rasagiline (Azilect®) not be listed.



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