

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Levodopa / Carbidopa / Entacapone

Product:

LEVODOPA / CARBIDOPA /
ENTACAPONE (Stalevo®)
50mg/12.5mg/200mg,
100mg/25mg/200mg, and
150mg/37.5mg/200mg tablets

Class of drugs:

Anti-parkinsonian agent

Indication:

Treatment of Parkinson's disease

Manufacturer:

Novartis Pharmaceuticals Canada Inc.

CED Recommendation

The CED recommended that levodopa/carbidopa/entacapone (Stalevo) be funded as a Limited Use Benefit on the Ontario Drug Benefit Formulary. The CED noted that this new combination product appears to be similar in efficacy and safety as the concurrent use of its individual component medications.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer approved funding for levodopa/carbidopa/entacapone (Stalevo).

Status

Listed on the Ontario Drug Benefit Formulary as a Limited Use Benefit.

Highlights of Recommendation:

- ◆ Stalevo is a tablet that combines three medications, levodopa, carbidopa and entacapone, used for the treatment of Parkinson's disease.
- ◆ A combination tablet with levodopa and carbidopa as well as a single-agent tablet for entacapone are already funded on the Formulary.
- ◆ Evidence suggests that the efficacy and safety of levodopa/carbidopa/entacapone (Stalevo) is similar to the individual component medications combined.
- ◆ Levodopa/carbidopa/entacapone (Stalevo) costs \$1.56 per tablet, which is similar to the stand-alone entacapone tablet. Using levodopa/carbidopa/entacapone (Stalevo) as a substitute in patients who require all the individual agents should result in cost-savings. However, funding levodopa/carbidopa/entacapone (Stalevo) may increase the risk of inappropriate use in patients with early Parkinson's disease, where entacapone has not been shown to be cost-effective. This inappropriate use may negate some of the savings generated by the lower acquisition cost, and prescribers should be encouraged to prescribe appropriately.
- ◆ Single-agent entacapone is currently available as a Limited Use Benefit on the Formulary for patients whose Parkinson's disease cannot be adequately managed by levodopa/carbidopa. The Committee noted that levodopa/carbidopa/entacapone (Stalevo) should be reimbursed in a similar manner as single-agent entacapone.
- ◆ **Overall, the Committee noted that levodopa/carbidopa/entacapone (Stalevo) provides similar efficacy and safety as the combination use of its individual components.**

Background:

Parkinson's disease is a neurologic disorder that affects parts of the brain that control muscle movement. In Parkinson's disease, neurons that make a chemical called dopamine die or do not work properly. Dopamine sends signals that help coordinate body movements. The cause of Parkinson's disease is unknown. Symptoms may include tremor, stiffness, poor balance and coordination. As symptoms get worse, patients may have trouble walking, talking or doing simple tasks.

There is no cure for Parkinson's disease. The goal of treatment is to control symptoms. Levodopa is one of the primary drugs used to manage symptoms. It increases the brain's supply of dopamine, which may improve movement and balance. Levodopa is always used in combination with carbidopa to reduce the side effects of levodopa and to make levodopa work better. Carbidopa alone has no benefit. Long-term use of levodopa can result in complications called motor fluctuations and dyskinesia. Motor fluctuations are a group of symptoms that include the "wearing off" effect (when the medication wears off before the next scheduled dose). Dyskinesia consists of abnormal involuntary movements that cause rapid jerking or slow and extended muscle spasms. Sometimes, adding entacapone may help to prolong and increase the effect of levodopa and is used in patients with motor fluctuations who have "wearing off" periods at the end of their doses of levodopa. Entacapone has no effect on its own.

Levodopa/carbidopa/entacapone (Stalevo) is indicated for the treatment of Parkinson's disease to substitute for levodopa/carbidopa and entacapone previously administered as separate products. It is also indicated to replace levodopa/carbidopa therapy in patients who experience the "wearing off" effect.

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Detailed Discussion:

- ◆ The Committee reviewed four bioequivalence studies evaluating the drug delivery of levodopa/carbidopa/entacapone (Stalevo) versus the three individual component medications. In terms of drug absorption into the body, levodopa/carbidopa/entacapone (Stalevo) was shown to be similar to the concurrent administration of the three separate component drugs. Thus, levodopa/carbidopa/entacapone (Stalevo) is expected to provide comparable efficacy and safety as the individual agents combined.
- ◆ The Committee also reviewed two randomized controlled clinical studies. One study was conducted in patients with Parkinson's disease who were experiencing end-of-dose "wearing off" effect while taking levodopa/carbidopa. The study showed comparable clinical improvements between patients treated with levodopa/carbidopa/entacapone (Stalevo) and those who received levodopa/carbidopa plus entacapone as separate products.
- ◆ The second study compared levodopa/carbidopa/entacapone (Stalevo) to levodopa/carbidopa alone in patients with Parkinson's disease and minimal motor fluctuations. Compared with levodopa/carbidopa, levodopa/carbidopa/entacapone (Stalevo) was found to be associated with greater improvements on measures of quality of life and activities of daily living.
- ◆ The two clinical studies found no significant differences in adverse events between levodopa/carbidopa/entacapone (Stalevo) and the individual products.
- ◆ There is no evidence that patients' adherence to treatment is improved with the combination tablet versus the separate agents.
- ◆ Entacapone is currently funded as a Limited Use Benefit in patients with 25% of the waking day in the off state despite maximally tolerated doses of levodopa. The Committee noted that entacapone has not been shown to slow disease progression and its efficacy and cost-effectiveness in early Parkinson's disease have not been established.
- ◆ Levodopa/carbidopa/entacapone (Stalevo) costs \$1.56 per tablet, which is less than the total cost of the individual products. However, the cost-savings may be negated if the combination product is used inappropriately in early disease.
- ◆ In light of the above, the Committee recommended that levodopa/carbidopa/entacapone (Stalevo) be funded as a Limited Use Benefit on the Formulary with the same clinical criterion as that for entacapone.

Limited Use Criteria:

The Committee recommended that levodopa/carbidopa/entacapone (Stalevo) be funded as a Limited Use Benefit according to the following clinical criterion:

For the treatment of patients with Parkinson's disease with 25% of the waking day in the off state despite maximally tolerated doses of levodopa.

CEDAC Recommendation:

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

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that levodopa/carbidopa/entacapone (Stalevo) be listed in a similar manner as drug plans list entacapone.



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