

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

LEVODOPA/CARBIDOPA/ENTACAPONE (Stalevo[®] – Novartis Pharmaceuticals Canada Inc.)

Description:

Stalevo[®] is a fixed dose combination of levodopa, carbidopa (a dopa-decarboxylase inhibitor, DDCI) and entacapone (an inhibitor of catechol-O-methyltransferase). Stalevo is indicated for the treatment of idiopathic Parkinson's disease to substitute for immediate-release levodopa/carbidopa and entacapone previously administered as individual products. It is also indicated to replace immediate-release levodopa/carbidopa therapy (without entacapone) when patients experience the signs and symptoms of end of dose "wearing off" (only recommended when patients are taking a total daily dose of levodopa of 600 mg or less and not experiencing dyskinesias).

Dosage Forms:

Tablets containing levodopa/carbidopa/entacapone in the following combinations: 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg and 150 mg/37.5 mg/200 mg. The maximum recommended daily dose of entacapone is 1600 mg and therefore the maximum Stalevo dose is 8 tablets per day.

Recommendation:

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

Reasons for the Recommendation:

1. All strengths of Stalevo are priced at \$1.56 per tablet which is similar to entacapone (Comtan[®]) 200 mg tablets. As a result, the use of Stalevo to replace a regimen of levodopa/carbidopa and entacapone would be less costly (saving the cost of levodopa/carbidopa).
2. Health Canada accepted that the mean plasma levels of levodopa, carbidopa and entacapone from Stalevo are similar to the individual components administered separately.

Summary of Committee Considerations:

The Committee considered a systematic review of two randomized controlled trials (RCTs) in patients with idiopathic Parkinson's disease (N=361). One six-week trial compared Stalevo to entacapone plus the patients' regular regimen of levodopa/DDCI in patients experiencing end-of-dose "wearing off" phenomenon while taking levodopa/DDCI. This trial reported no statistically significant differences between the two treatment groups in the Unified Parkinson's Disease Rating Scale (UPDRS), or in motor fluctuations.

A 12 week, double-blind RCT which compared Stalevo to levodopa/carbidopa in patients with minimal disabling motor fluctuations, was also considered. Stalevo was associated with statistically significant improvements in quality of life and the total score of the UPDRS, but the clinical relevance of these findings is questionable. There were no statistically significant differences between Stalevo and levodopa/carbidopa for incidence of dyskinesia.

There was no evidence from either RCT that Stalevo improved patient compliance compared with the use of the individual agents. There were no statistically significant differences observed in adverse event rates between Stalevo and the comparator arm in either trial.

Four open-label, randomized bioequivalence trials compared plasma concentrations of Stalevo to its individual components administered separately. Results indicated that Stalevo met most of the area under the curve and plasma concentration requirements of Health Canada to establish bioequivalence. Despite some pharmacokinetic deviations documented in these four bioequivalence trials, Health Canada concluded that the efficacy and safety of the immediate-release fixed combination tablet were not expected to differ from the safety and efficacy of co-administered levodopa/carbidopa and entacapone.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The Committee was aware of ongoing trials in patients with early Parkinson's Disease, however, the effectiveness of Stalevo in this population has not yet been established. Stalevo is an appropriate option for patients experiencing end-dose "wearing-off" phenomenon after levodopa/carbidopa are optimized at the maximum tolerable dose. The use of Stalevo prior to maximizing the levodopa/carbidopa dose is unlikely to be cost-effective.
3. A number of agents are available as adjunctive therapy to levodopa/carbidopa for patients with Parkinson's Disease. Drug plans should consider a drug class review of these agents to assess their relative effectiveness, harms, cost and place in therapy. In particular, given that ongoing studies are assessing the effectiveness of entacapone in early Parkinson's disease, and that market expansion into this area is likely, the Committee had concern regarding the unrestricted listing status of entacapone in some jurisdictions.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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Common Drug Review