

B.C. Ministry of Health Services Drug Coverage Decision

About PharmaCare	B.C. PharmaCare helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.
PharmaCare Coverage	The Ministry of Health Services (Ministry) makes PharmaCare coverage decisions by considering existing PharmaCare policies, programs and resources and the evidence-based recommendations of an independent advisory body called the Drug Benefit Council (DBC). The DBC's advice to the Ministry is based upon a review of many considerations, including available clinical and pharmacoeconomic evidence, clinical practice and ethical considerations, and the recommendations of the national Common Drug Review, when applicable.
Inside	Page 1 includes the Ministry's decision and reasons in wording that is easier for readers without a medical background to understand. Page 2 summarizes the DBC recommendation, the Ministry's decision and the reasons for the Ministry's decision.

Levodopa-carbidopa-entacapone (Stalevo®) for hard-to-treat Parkinson's Disease

Understanding the DBC Recommendation and PharmaCare Coverage Decision

Background

- Patients with **Parkinson's Disease (PD)** often have shaking (tremor), stiffness and slow movement, from a lack of the chemical called dopamine. PD affects the nerve cells in the brain to cause a decrease in dopamine release.
- **Levodopa plus carbidopa plus entacapone** combination tablet has the trade name **Stalevo®**.
 - It belongs to the class of drugs called **anti-parkinsonian dopaminergic agents**.
 - Levodopa helps treat the symptoms of PD by increasing the levels of dopamine in the brain. The effect of levodopa may begin to wear off after a long time, making the symptoms worse. This is called **"end-of-dose wearing off."**
 - Carbidopa and entacapone help to improve the effect of levodopa by preventing its break-down.
- Other drugs used to improve the effect of levodopa are called **dopa decarboxylase inhibitors**.

Why was this drug reviewed?

- Drug company request.

What did the review find?

- One study in patients with PD and signs of "end-of-dose wearing off" shows that levodopa plus carbidopa plus entacapone has the same effect on daily activities and movement control as separate products (levodopa plus a dopa decarboxylase inhibitor and entacapone).
- In patients with PD and slight movement control problems, one study shows that levodopa plus carbidopa plus entacapone is better than levodopa

plus carbidopa at improving symptoms and quality of life. The difference is small and the impact is not known.

- The number of side effects with levodopa plus carbidopa plus entacapone is no different than separate products (levodopa plus a dopa decarboxylase inhibitor and entacapone) or a single product (levodopa plus carbidopa).
- Studies do not show that patients take their drugs more regularly if they are taking a single product, e.g. levodopa plus carbidopa plus entacapone.
- The combination of levodopa plus carbidopa plus entacapone is less costly than buying the drugs separately.

What decision was made?

- Levodopa plus carbidopa plus entacapone (Stalevo®) will have **limited coverage** for the treatment of PD for:
 - Patients with a poor response to levodopa plus carbidopa even after adjusting the dose. Poor response is defined as noticeable "wearing off" and/or severe side effects affecting movement.

Key Term(s)

- **Limited coverage** drugs are not normally considered the first choice in treatment, or other drugs may offer better value. To receive coverage, the patient's physician must submit a Special Authority request to PharmaCare. If the request is approved, the drug is covered up to the usual PharmaCare coverage limits. Actual reimbursement depends on the rules of a patient's PharmaCare plan including any annual deductible requirement.

This document is intended for information only. It does not take the place of advice from a physician or other qualified health care provider.

Please visit us online to find out more about the Pharmaceutical Services Division and the PharmaCare program at www.health.gov.bc.ca/pharmacare. To find out more about how drugs are considered for PharmaCare coverage, visit www.health.gov.bc.ca/pharmacare/formulary.



Levodopa-carbidopa-entacapone (Stalevo[®]) for hard-to-treat Parkinson's Disease

Drug Class

- Anti-parkinsonian dopaminergic agent

Available Dosage Forms

- 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 mg tablets (combination product levodopa plus carbidopa plus entacapone)

Sponsor/Requestor

- Novartis Pharmaceuticals Canada Inc.

Submission (Request) to PharmaCare

- Drug review of levodopa plus carbidopa plus entacapone (Stalevo[®]) for the following Health Canada approved indications:
 - For the treatment of idiopathic Parkinson's disease to substitute for immediate-release levodopa plus carbidopa and entacapone previously administered as individual products. It is also indicated to replace immediate-release levodopa plus 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).

Drug Benefit Council (DBC)

Recommendations

- That levodopa plus carbidopa plus entacapone (Stalevo[®]) be listed as a limited coverage drug for the treatment of idiopathic Parkinson's disease with the following criteria:
 - Patients with an inadequate response (defined as significant "wearing off" and/or severe motor complications, i.e. fluctuations) after alterations of levodopa plus carbidopa doses.

Reasons for the Ministry of Health Services Decision

- A literature search identified two randomized controlled trials (RCTs) of 6 and 12 weeks duration. The trial of 6 weeks duration compared levodopa plus carbidopa plus entacapone to levodopa plus dopa decarboxylase inhibitor (DDCI) and entacapone in patients experiencing end-of-dose "wearing off" while on levodopa plus DDCI. The trial of 12 weeks duration compared levodopa plus carbidopa plus entacapone with levodopa plus carbidopa in patients with minimal disabling motor fluctuations. A total of 361 patients participated in the two RCTs.
- In the 6-week trial comparing levodopa plus carbidopa plus entacapone to levodopa plus DDCI plus entacapone in patients experiencing end-of-dose "wearing off" while on levodopa plus DDCI, the two groups showed similar improvement on Unified Parkinson's Disease Rating Scale (UPDRS) Part II activities of daily living scores (-3.2 versus -2.8 point change) and UPDRS Part III motor function scores (-7.0 versus -7.1 point change).
- In the 12-week trial comparing levodopa plus carbidopa plus entacapone to levodopa plus carbidopa in patients with minimal disabling motor fluctuation, there was a statistically significant improvement in the quality of life scores and UPDRS in the levodopa plus carbidopa plus entacapone treatment arm, but the clinical significance of these findings is uncertain. Blinding of the study was likely compromised due to higher incidence of urine discoloration in the levodopa plus carbidopa plus entacapone treatment arm.
- Incidence of adverse effects was not statistically significant between levodopa plus carbidopa plus entacapone and comparators in RCTs.
- There was no evidence from RCTs that levodopa plus carbidopa plus entacapone combination product improved patient compliance compared to individual products.
- Cost of levodopa plus carbidopa plus entacapone is less than the cost of levodopa plus carbidopa and entacapone administered separately.

Decision and Status

- **Limited coverage** as per Special Authority criteria set forth in the DBC recommendation (on this page).
- Effective June 5, 2009.

Key Term(s)

- **Limited coverage** drugs are not normally considered the first choice in treatment, or other drugs may offer better value. To receive coverage, the patient's physician must submit a Special Authority request to PharmaCare. If the request is approved, the drug is covered up to the usual PharmaCare coverage limits. Actual reimbursement depends on the rules of a patient's PharmaCare plan including any annual deductible requirement.