



CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

LEVODOPA/CARBIDOPA (Duodopa™ – Solvay Pharma Inc.) Indication: Parkinson's Disease

Description:

Duodopa is a combination of levodopa and carbidopa in a gel formulation which is administered directly into the small intestine as a continuous infusion. It is approved for use by Health Canada for treatment of advanced Parkinson's disease in which satisfactory control of severe, disabling motor fluctuations and hyperkinesia or dyskinesia cannot be achieved with available combinations of Parkinson medicinal products. It has been issued a Notice of Compliance with Conditions from Health Canada, pending the results of studies to verify its clinical benefit.

Dosage Forms:

Supplied in 100 mL cassette containing levodopa 20 mg/mL and carbidopa 5 mg/mL (4:1 ratio) as a gel formula. The maintenance dose ranges from 20 mg to 200 mg levodopa/hour over a 16 hour day, with additional bolus doses as required.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Duodopa not be listed.

Reasons for the Recommendation:

1. The key reason for the recommendation was the manufacturer's reported incremental cost per quality adjusted life year (QALY) estimate for Duodopa of [REDACTED] to [REDACTED] compared with conventional oral drug therapies. The manufacturer requested that specific results from the economic evaluation remain confidential pursuant to the CDR Confidentiality Guidelines. Other published cost per QALY estimates for Duodopa were reported at approximately \$1 million dollars.
2. The quality of two trials considered by the Committee was limited by open-label designs, high proportions of withdrawals in trials of small sample size and patient populations that are not representative of those who are most likely to use Duodopa. Therefore, given concerns with the quality of these trials, the relevance of the results was limited.

Summary of Committee Considerations:

The Committee considered the results of a systematic review that included two randomized, open-label, crossover trials evaluating the effects of Duodopa in patients with advanced Parkinson's disease and

severe motor complications. The DIREQT trial (n=25) compared Duodopa with patients' pre-study conventional therapy. Treatment sequences were three weeks. The primary outcomes in the DIREQT trial were Unified Parkinson's Disease Rating Scale (UPDRS) item scores and time spent in various motor states as assessed by video recording. Quality of life was also measured in the DIREQT trial. In the NPP-001-99 trial (n=16), Duodopa was compared with long-acting levodopa/carbidopa, and the short-acting formulation was given to patients as needed. Long-acting levodopa/carbidopa is not considered an appropriate comparator in this patient population.

The validity of results from the two trials was limited by a number of factors, including open-label designs and high proportions of withdrawals in trials of small sample size. Furthermore, the generalizability of the study conclusions are limited because the patient populations included are not representative of those who are most likely to use Duodopa. It is likely that patients using Duodopa will be over age 70, i.e., those who do not qualify for deep brain stimulation, but these trials were conducted in a younger population; with an average age ranging from 60 to 68 years across trials and treatment groups. In both studies, Duodopa was administered by a nasoduodenal tube rather than by the intended PEG tube administration of the marketed product. It is not clear if the effect would be similar for nasoduodenal and PEG administration. Therefore, given concerns with trial quality, the relevance of the results was limited.

In the DIREQT trial, there were statistically significant improvements in quality of life, UPDRS scores (scores range from 0 to 199) and motor function with Duodopa compared with conventional drug therapy. Quality of life, measured by the 39-item Parkinson's Disease Questionnaire (scores range from 0 to 100), was statistically significantly improved with Duodopa compared with conventional treatment (median difference = -9.0, $P < 0.01$). Motor function, measured as the percentage of "on-time" during video recording, was statistically significantly higher with Duodopa compared with conventional treatment [median difference (range) = 4.5% (-14.7 to 63.2); $P < 0.01$]. The percentage of "off-time" was statistically significantly lower with Duodopa compared with conventional drug therapy (median difference = -8.1%; $P < 0.01$). The magnitude of between-treatment differences for all measures was considered clinically important. However, the lack of blinding and the use of per-protocol analysis for most outcomes may have biased estimates of efficacy in favour of Duodopa.

The proportions of patients experiencing serious adverse events and adverse events were similar between treatment groups in both studies. Common adverse events included well-documented effects of levodopa/carbidopa involving the gastrointestinal tract (i.e., constipation, diarrhea) and the central nervous system (i.e., depression, insomnia, somnolence), as well as administration-related complications (dislocated tubes and intolerance or dislike of the nasoduodenal tube or pump). Withdrawal due to an adverse event occurred in three Duodopa patients and no patients in the conventional treatment group in the DIREQT trial.

The Committee also noted the results of two small (n=13 and 22) uncontrolled studies with a pre-post design, which provided clinical inputs for the manufacturer's economic evaluation. Results were reported over time periods ranging from six months to two years. Statistically significant improvements were observed for only subjective patient-reported outcomes such as quality of life, activities of daily living, and motor function (measured as "off-time" and "on-time"). There were no statistically significant improvements in clinician-assessed motor function as measured by the UPDRS. The validity of these studies is limited due to their lack of control group and reliance on observed-case analysis when data were missing.

In the cost-utility analysis submitted by the manufacturer, Duodopa was compared with conventional oral drug therapies (i.e., levodopa/carbidopa, cabergoline, pramipexole, pergolide, entacapone, amantadine sulphate, and/or selegiline) for the treatment of advanced Parkinson's disease over a five-year period.

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The manufacturer's results were highly dependent on the study selected to inform the clinical input parameters, with the manufacturer reporting incremental cost per QALY estimates for Duodopa ranging from approximately [REDACTED] to [REDACTED]. The manufacturer requested that specific results from the economic evaluation remain confidential pursuant to the CDR Confidentiality Guidelines.

The cost of Duodopa is \$166 per day; in comparison, oral forms of levodopa/carbidopa cost less than \$3 per day.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. A Notice of Compliance with Conditions was issued by Health Canada in March 2007, pending additional evidence, including results of a 12-week double-blind RCT where Duodopa is administered through a PEG tube.
3. This document has been edited to remove confidential information at the manufacturer's request in conformity with the CDR Confidentiality Guidelines.

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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