

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

APOMORPHINE HYDROCHLORIDE (MOVAPO — PALADIN LABS INC.)

Indication: Parkinson's disease

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that apomorphine hydrochloride (apomorphine) be reimbursed for the acute, intermittent treatment of hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes) in patients with advanced Parkinson's disease (PD), if the following criterion and conditions are met:

Criterion:

- Apomorphine should only be used as adjunctive therapy in patients who are receiving optimized PD therapy (levodopa and derivatives and dopaminergic agonists) and still experiencing “off” episodes.

Conditions:

- Patients treated with apomorphine should be under the care of a physician with experience in the diagnosis and management of PD.
- Reduction in price.

Service Line: CADTH Drug Reimbursement Recommendation

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Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that apomorphine hydrochloride (apomorphine) be reimbursed for the acute, intermittent treatment of hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes) in patients with advanced Parkinson's disease (PD), if the following criterion and conditions are met:

Criterion:

- Apomorphine should only be used as adjunctive therapy in patients who are receiving optimized PD therapy (levodopa and derivatives and dopaminergic agonists) and still experiencing “off” episodes.

Conditions:

- Patients treated with apomorphine should be under the care of a physician with experience in the diagnosis and management of PD.
- Reduction in price.

Reasons for the Recommendation:

1. In three randomized, double-blind, placebo-controlled trials (APO 202 [N = 29], APO 301 [N = 17], and APO 302 [N = 62]), a statistically and clinically significant improvement in motor function based on the primary efficacy parameter, Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) motor score from baseline to 20 minutes post-dose, was found with apomorphine compared with placebo for the treatment of intermittent, “off” episodes in patients with advanced PD.
2. At the submitted unit price of \$42.95 per 3 mL (30 mg) pen of apomorphine, the base-case results of the manufacturer's cost-utility analysis reported an incremental cost-utility of \$72,705 per quality-adjusted life-year (QALY). The CADTH Common Drug Review (CDR) identified several key limitations with the model submitted by the manufacturer. Reanalyses by CDR concluded that, at the submitted price, the base-case incremental cost-utility ratio (ICUR) for apomorphine plus standard of care (SoC) compared with SoC alone is \$242,004 per QALY. Apomorphine had a 0% probability of being cost-effective at a willingness-to-pay threshold of \$100,000 per QALY. A price reduction of almost 50% would be required for apomorphine to achieve an ICUR of less than \$100,000 per QALY, and 65% to cost less than \$50,000 per QALY.

Of Note:

CDEC noted that patients were considered eligible for inclusion in the APO 202 study if they experienced “on/off” fluctuations averaging at least two hours of daily “off” time (either “on/off” or “wearing off” patterns) despite optimal treatment with at least two drugs (typically levodopa/carbidopa with a direct dopamine agonist) for at least 30 days prior to study entry.

Discussion Points:

- CDEC noted that while a reduction in the UPDRS-III motor score is important and is associated with a relief of acute discomfort, the UPDRS-III score reflects only a short-term resolution of the symptoms of PD. Change in UPDRS-III motor score may be considered a surrogate for long-term outcomes, such as the ability to maintain independence in activities of daily living, relief of

caregiver burden, or the avoidance of institutional care. Data correlating UPDRS-III motor score changes to these functional parameters would be of value to assess the validity of the UPDRS as a surrogate outcome.

- CDEC noted that there is an important concern that “off” periods in PD cause significant caregiver burden and compromise patient independence, which could hasten institutional care for such patients. Input from patient groups supports the need for therapy to treat “off” periods. Other treatments for advanced PD are invasive and expensive and are usually reserved for patients with more advanced disease.
- CDEC noted that discontinuation of apomorphine therapy would be best managed at the discretion of the treating physician.

Background:

Apomorphine has a Health Canada–approved indication for the treatment of acute, intermittent hypomobility and “off” (“end-of-dose wearing off” and unpredictable “on/off”) episodes in patients with advanced PD. Apomorphine belongs to the class of post-synaptic dopamine agonists and is available in Canada as 3 mL pre-filled, disposable, multi-dose pens at a strength of 10 mg/mL. The Health Canada–approved dosage is 0.2 mL (2 mg) to 0.6 mL (6 mg) per dose, to be administered subcutaneously as an adjunct to regular oral anti-PD medications.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of apomorphine and a critique of the manufacturer’s pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience treating patients with PD and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by PD.

Patient Input Information

Two patient groups responded to the call for patient input for this CDR review: Parkinson Canada and Parkinson Society British Columbia. Information was gathered through an online survey done on patients and caregivers; through helpline, referral service, and online resources for PD patients; and from a clinical expert in PD who was a strong advocate for apomorphine use. The following is a summary of key input from the perspective of the patient groups:

- The characteristic symptoms of PD include varying degrees of motor, gait, and cognitive impairments. In addition, patients suffer from a loss of confidence in maintaining family and social life as well as performing everyday chores and recreational activities, and increased dependency on caregivers. The loss of confidence is largely a result of “off” episodes, when a resurgence of motor and non-motor symptoms of PD appear which can be of “treatment wearing off” or “unpredictable off” in nature. This was considered an unmet need by the patients.
- Levodopa is the most common therapy currently used; however, its effects wear off quickly and frequent adjustment in dosage and meals is needed due to the chemical interaction between the drug and meals. Continuous infusion of Duodopa (mixture of levodopa and carbidopa) is sometimes prescribed to improve the bioavailability of levodopa. Deep brain stimulation is a more invasive surgical procedure. The two latter interventions are associated with high cost, difficulty in access, and longer recovery time.
- The majority of the patients indicated a preference for medications that are fast-acting and durable and reduce “off” times in addition to minimizing PD symptoms and drug-associated side effects. Among the few respondents with experience using apomorphine injection, an improvement in “treatment wearing off” and reduction in “off” times was reported.

Clinical Trials

There were three double-blind, randomized, placebo-controlled trials that met the inclusion criteria of the systematic review conducted by CDR. These included one phase II, parallel-group, four-week trial (APO 202 [N = 29]) and two phase III trials, of which one had crossover design (APO 301 [N = 17]) and the other was parallel-group (APO 302 [N = 62]) in nature. The phase II trial was

conducted among treatment-naive patients, whereas patients in the phase III trials were subjected to treatment for at least three months prior to the study period. All three trials were conducted in late-stage PD patients (Hoehn and Yahr scale 2 to 4) who were on optimal anti-PD medications. In the APO 202 study, a mean dose of 5.8 mg/dose was administered by the patients in response to spontaneous “off” episodes during a four-week outpatient period, after a mean therapeutic dose of 5.4 mg/dose was found effective in eliciting $\geq 90\%$ of the response compared with levodopa during an in-patient dose-titration period. The APO 301 study consisted of a single, alternate dose of apomorphine (mean 3.9 mg/dose) or placebo in a crossover manner. Patients in the APO 302 study were randomized in a 2:2:1:1 ratio to receive a single dose of apomorphine or equivalent volume-matched placebo at their regular dose (mean 4.6 mg/dose) or 2 mL extra (5.8 mg/dose).

A limitation common to all trials was the potential of unblinding of treatment allocation among participants due to the clinically obvious treatment effects and side effects associated with apomorphine treatment. The sample size was small, particularly in the APO 202 and APO 301 studies. The length of double-blind treatment was also not long enough to capture the complete profile of adverse events (AEs); therefore, results from the longer term open-label studies should be considered. Finally, all trials were placebo-controlled, and no active comparator trials met the review criteria.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- UPDRS-III: A 14-item subscale of UPDRS scored on a five-point scale (0 to 4, total score of 56, higher scores indicate worse symptoms) and designed to evaluate motor disability and impairment in patients with PD.
- Dyskinesia Rating Scale: A five-point scale (0 to 4, higher scores indicate worse dyskinesia) used to rate the severity and type of dyskinesia interfering with the activities of daily life and based on three tasks: walking, putting on a coat, and lifting a cup for drinking.
- Hand-tapping test: A scoring system to determine upper limb dyskinesia by counting the numbers of hand taps done alternatively with both hands in a minute.
- Webster step-seconds test: A scoring system to evaluate overall disability from gait disturbances by measuring the time and number of steps taken to walk 15 feet from a sitting position and back.
- Patient-recorded daily “off” time: The frequency and duration of daily “off” episodes per day recorded by patients in diaries.

In all three studies, change in UPDRS-III score from pre-dose “off” state to 20 minutes post-dose “on” state was the primary efficacy outcome. The secondary efficacy outcomes varied by the trials and involved one or more of the following: UPDRS-III up to 60 or 90 minutes post-dose, Dyskinesia Rating Scale, hand-tapping score, Webster step-seconds test, and patient-recorded outcomes on perceived “on” and “off” episodes. No outcomes related to quality of life were reported. Patients emphasized the reduction in “off” times (“unpredictable off” or “treatment wearing off”) as an important measure of treatment efficacy, which was captured in one study.

Efficacy

In APO 202, 301, and 302, there was a statistically significant decrease in per cent mean UPDRS-III score from pre-dose values at 20 minutes by 61.7%, 47.4%, and 58.7%, respectively, in the apomorphine-treated group compared with the placebo group (all P values ≤ 0.0001). The corresponding decreases in post-dose mean scores in the three trials were 23.9, 20.0, and 24.2, respectively, all of which were greater than the reported minimal clinically important differences for UPDRS-III (–5 points to –6.5 points).

The following secondary efficacy outcomes were reported in the trials; however, the lack of control for multiple comparisons does not allow for statistical comparisons between the treatment arms. In APO 301, there was a decrease in per cent mean UPDRS-III score at 10 minutes (35.9%, $P = 0.004$) and 60 minutes (30.2%) post-dose in the apomorphine-treated group compared with the placebo group. In APO 302, the per cent decrease in the apomorphine-treated group compared with the placebo group was statistically significant at 10 minutes (31.1%, $P < 0.0001$) post-dose but not at 90 minutes (0.8%, $P = 0.9$).

In the APO 202 trial, there was an increase in median dyskinesia score post-dose during the in-patient (1 versus 0 in the apomorphine-treated group and placebo-treated group, respectively) and outpatient phase (1.6 versus 1.2 in the apomorphine and placebo groups, respectively). In both APO 301 and APO 302, median disease rating scale score increased compared with placebo at 10 and 20 minutes post-dose, but not at 60 or 90 minutes.

Hand-tapping score was measured only in APO 202, and a numerically greater increase in post-dose value was found in the apomorphine-treated group compared with the placebo group (mean score change 109 in apomorphine versus -12 in placebo).

The Webster step-seconds test was measured in APO 202 and APO 302. In APO 202, a median decrease of 402 (65%) was seen post-dose in apomorphine-treated patients without any changes in placebo. In APO 302, the median step-seconds score decreased at all time points up to 40 minutes in both treatment arms; however, the decrease was numerically greater in the apomorphine-treated group compared with the placebo group.

Duration of “off” episodes per day was measured in APO 202 only, and a mean decrease of 1.7 hours from baseline was seen in the apomorphine-treated group without any concomitant change in the placebo group. The mean decrease was within the minimal clinically important difference for daily “off” hours (1 to 1.8 hours); however, a statistical inference should not be made due to the lack of control for type I error.

Mean time to response, that is, onset of “on” state following treatment, decreased numerically in the apomorphine-treated group compared with the placebo group (22.1 versus 44.8 minutes) in APO 202. In APO 301 and APO 302, the differences in mean time to response were not as high when missing values and censoring were taken into account.

Harms (Safety and Tolerability)

In all three trials, the AEs reported were known side effects of apomorphine, were mild to moderate in severity, and included injection site reactions, yawning, dyskinesia, fatigue, somnolence, dizziness, nausea/vomiting, and fall. However, the trials were of short duration; therefore, a complete AE profile may not have been identified. More than 85%, 17%, and 40% patients in the APO 202, APO 301, and APO 302 trials, respectively, experienced one or more of these AEs. One serious adverse event (SAE) and two cases of treatment withdrawal due to AEs (WDAEs) were registered in APO 202; none was related to study treatment. Three patients receiving placebo discontinued treatment in APO 301 and APO 302 in total, not due to AEs. The frequency of orthostatic hypotension was found at a higher frequency among apomorphine-treated patients in APO 301 and APO 302 (31% and 34%, respectively) compared with the placebo group. The frequency of dyskinesia also increased among apomorphine-treated patients in all trials; however, they were mild to moderate in severity.

Two long-term, open-label trials, APO 303 and APO 401, conducted for six and 12 months, respectively, reported the same AEs in the majority (> 90%) of the patients. The rate of study discontinuation was 41% and 78% in these studies, respectively, approximately one-third of which were due to WDAEs. Four cases of SAEs were reported in APO 303 and 199 in APO 401, one and 27 of which were treatment-related, respectively. Orthostatic hypotension was seen in 20% to 30% patients in both open-label trials, with a higher frequency among apomorphine-treated patients.

Cost and Cost-Effectiveness

Apomorphine was approved by Health Canada as a 3 mL (30 mg) pre-filled multi-dose pen for injection and a 2 mL (20 mg) ampoule for injection. The manufacturer requested reimbursement only of the multi-dose pen, stating that it did not intend to market the ampoule in Canada. The price of apomorphine is \$42.95 per 3 mL (30 mg) pre-filled multi-dose pen (\$1.43 per mg). The recommended starting dose of apomorphine is 0.2 mL (2 mg) as needed to treat recurring “off” episodes, titrated by 0.1 mL every few days on the basis of effectiveness and tolerance, up to a maximum dose of 0.6 mL (6 mg). The total daily dose should not exceed 2 mL (20 mg). Apomorphine pens should be discarded 48 hours after first use, and it is recommended that a non-5HT₃ antagonist antiemetic should be started at least two days prior to the initial apomorphine dose.

The manufacturer submitted a cost-utility analysis comparing apomorphine (with concomitant domperidone) as an adjunct to SoC oral PD therapy (e.g., levodopa, dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors) against SoC alone for the treatment of “off” episodes in patients with advanced PD. The manufacturer’s base case was a probabilistic

analysis conducted from the perspective of a Canadian health care payer over a five-year time horizon, with costs and benefits after one year discounted at a rate of 1.5%. The model consisted of four “off” health states based on quartiles of waking time spent in “off” state and death. Patients entered the model in one of the four health states, those in the apomorphine group transitioned to a less severe “off” state after the first one-year cycle based on the findings of a published systematic review, while those in the SoC group remained in their original “off” state. With the exception of mortality, no transitions occurred after the first cycle. For the purpose of utility estimates and resource use, all patients were assumed to have a Hoehn and Yahr stage of 3.6 based on the same systematic review; Hoehn and Yahr stage was not otherwise considered in the model. As SoC was assumed to be the same between groups, only AEs associated with apomorphine were included.

CDR identified several key limitations with the model submitted by the manufacturer. Firstly, the model structure did not consider Hoehn and Yahr stages independently and the relationship between discrete Hoehn and Yahr stages and “off” time, which may impact efficacy, dosing, disease progression, mortality, AEs, health care resource use, or utilities based on severity of disease. Furthermore, the appropriateness of the systematic review was deemed highly uncertain due to the heterogeneity of the patient populations in the included studies and oversimplified meta-analysis methods. Moreover, the model did not allow for treatment discontinuation, disease progression, or the attenuation of response to apomorphine over time. Finally, the consideration of dose of apomorphine in the model was inconsistent with the Health Canada–recommended dose in the product monograph.

The CDR base-case reanalysis considered changes to the following parameters: lower reduction in “off” time, inclusion of disease progression (as possible given the model structure), and increasing the daily dose to 15 mg daily. CDR was unable to test the impact of a model structure that considered distinct Hoehn and Yahr states and discontinuation of treatment, which leads to uncertainty in the cost-effectiveness of apomorphine. Reanalyses by CDR suggest that the ICUR for apomorphine plus SoC compared with SoC alone is \$242,004 per QALY. Apomorphine had a 0% probability of being cost-effective at a threshold of \$100,000 per QALY. A price reduction of almost 50% would be required for apomorphine to achieve an ICUR less than \$100,000 per QALY, and 65% to cost less than \$50,000 per QALY.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 13, 2017, Meeting

Regrets:

Three CDEC members did not attend.

Conflicts of Interest:

None