CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Apomorphine hydrochloride (Kynmobi — Sunovion Pharmaceuticals Canada Inc.)
Indication: The acute, intermittent treatment of "OFF" episodes in patients with Parkinson disease (PD).

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that apomorphine hydrochloride sublingual film (APO SL) should be reimbursed for the acute, intermittent treatment of OFF episodes in patients with PD only if the following conditions are met:

Conditions for Reimbursement

Initiation criteria

1. APO SL should only be used as adjunctive therapy in patients who are experiencing OFF episodes despite receiving optimized PD therapy (levodopa and derivatives and adjunctive therapy such as dopaminergic agonists or MAO-B inhibitors or amantadine derivatives).

Discontinuation criteria

1. Treatment with APO SL should be discontinued unless an improvement of at least 3.25 points is achieved in the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score measured within 30 to 60 minutes after a titrated dose of APO SL is administered. This assessment should occur not more than one year after APO SL has been titrated to a stable and tolerated dose. The maximum amount required should not exceed five films per day or 90 mg in total (whichever is reached first).

Prescribing conditions

1. Patients treated with APO SL should be under the care of a physician with experience in the diagnosis and management of PD.

Pricing conditions

1. The cost of reimbursing APO SL should not exceed the public drug plan cost of subcutaneous injection of APO (APO SC).

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Reasons for the Recommendation

1. The systematic review included one phase III, double-blind, randomized placebo-controlled trial of patients with idiopathic PD who had a clinically meaningful response to levodopa therapy and at least one OFF episode per day that lasted more than two hours (CTH-300, N = 109). Results of this study demonstrated that at week-12 patients allocated to receive APO SL had a statistically and clinically significant improvement in motor function, as measured by the MDS-UPDRS III score, after 30 minutes compared with those who received placebo (treatment difference of 7.6 points in favour of APO SL; 95% confidence interval [CI], –11.5 to –3.7, P = 0.0002). The validated threshold for detecting a clinically meaningful improvement in motor function using the MDS-UPDRS score is a decrease of 3.25 points. In addition, a statistically significant difference was observed in favour of APO SL versus placebo in the proportion of patients that achieved a full ON response within 30 minutes after drug administration at week 12 (predicted response rate: 35% for APO versus 16% for placebo; adjusted odds ratio 2.81; 95% CI, 1.04 to 7.64; P = 0.0426).
2. At the sponsor-submitted price, APO SL is less costly then APO SC. However, there is uncertainty with respect to the comparative clinical effectiveness between the two formulations due to the lack of direct clinical evidence. CADTH concluded that the efficacy of APO SL and APO SC is likely to be similar. Therefore, to remain cost-effective, the price of APO SL should not exceed that of APO SC.

Discussion Points

- CDEC noted that options for treatment of OFF periods in PD represent a significant need. OFF periods 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; however, CDEC noted that this therapy will not fully meet that

need due to the complexity of the dose titration process and increase in adverse effects compared with placebo. Some patients and caregivers will find the SL formulation advantageous.

- CDEC identified several significant limitations of the available evidence from the CTH-300 trial:
  - The single trial had a small sample (54 patients who received APO SL and 55 patients who received placebo), although the population who could potentially benefit is large because OFF episodes are common in patients with PD.
  - The population studied was an enrichment design. According to the FDA guidance for industry on the use of enrichment strategies in clinical trials, some empiric enrichment strategies can efficiently establish the effectiveness of a drug in a subset of the population; however, they cannot help physicians to prospectively identify patients who will have the measured effects.
  - A hierarchical testing approach was used for the analyses of the primary and secondary efficacy end points to control for multiplicity. Ten efficacy end points were included in this procedure. Statistical significance was not achieved for the secondary end point ranked third in hierarchical testing (percentage of patients at week 12 with a patient-rated full ON response within 30 minutes post-dose with a duration of at least 30 minutes). Therefore, statistical significance cannot be claimed for any end point ranked after this, including those most important to patients such as health-related quality of life (HRQoL).
  - CDEC noted that some clinical outcomes which are important to patients were not measured in this study, such as change in cognition and mood.
  - The reviewed trial studied 12 weeks of treatment in a chronic, progressive disease. Long-term efficacy and safety data are lacking.
- Patients treated with APO SL were more likely to withdraw due to adverse events (APO 27.8% versus placebo 7.3%) during the maintenance phase. In terms of harms of particular interest, the occurrence of gastrointestinal disorders, application site reactions (such as stomatitis, oral ulcers, and oral irritation), allergy or sensitivity to the formulation, daytime sudden onset of sleep, falls and injuries, and hypotension were higher in APO-treated patients compared with placebo.
- Dopamine agonists are associated with the development of impulse control disorders such as pathological gambling. Impulsive behaviour was identified as a notable harm in the CADTH review protocol and as a relevant harm by clinical experts. Occurrence of impulsive behavior was not reported in the CTH-300 study.
- CDEC noted that although a reduction in the MDS-UPDRS III motor score is important and is associated with relief of acute discomfort, the score reflects only a short-term resolution of the symptoms of PD. Change in MDS-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 MDS-UPDRS III motor score changes to these functional parameters would be of value to assess the validity of the MDS-UPDRS as a surrogate outcome.
- The committee noted that there were a number of limitations with the sponsor's submitted economic model that limited the reanalyses that could be conducted by CADTH. These limitations included the short model time horizon, failure to account for subsequent or adjunctive treatments, and not accounting for treatment waning or the natural disease progression with PD.
- CDEC heard from one clinical expert that therapy should not be initiated or continued in patients who have progressed to PD dementia.

Background

APO SL has a Health Canada indication for the acute, intermittent treatment of OFF episodes in patients with PD. APO is a non-ergot dopamine agonist. The precise mechanism of action of APO SL as a treatment for OFF episodes associated with PD is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D_2-type receptors within the caudate-putamen in the brain. APO SL is available as soluble film containing 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg APO per film. Dose titration is initiated with a single dose of 10 mg APO SL film when patients are in an OFF state. When the patient tolerates the dose but does not respond adequately, the patient should resume the usual PD medication, up-titrate the dose of APO SL at the next observed OFF period (generally within three days), and continue to titrate in a similar manner in 5 mg increments until an effective and tolerable dose is achieved, up to 30 mg. Doses should be separated by at least two hours and treatment should not be administered more than five films per day. The total daily dose should not exceed 90 mg.

Submission History

APO SL was first submitted to CADTH for a pre–notice of compliance review in February 2019. The proposed indication was for the acute, intermittent treatment of hypomobility, OFF episodes associated with PD including end-of-dose wearing OFF (including early morning OFF), partial, delayed, no ON, and unpredictable OFF. [redacted]. Therefore, the sponsor withdrew the application from the CDR process and CDEC did not review this drug. In June 2020, the sponsor refiled the submission to CADTH after APO SL received a notice of compliance from Health Canada on June 12, 2020. The approved indication is for acute, intermittent treatment of OFF episodes in patients with PD. The reimbursement criteria of APO SL film requested by the sponsor is the same as the Health Canada approved indication.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review which included one randomized controlled trial (RCT) of APO SL, an indirect comparison submitted by the sponsor, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with PD and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Five patient groups provided input for this review: (1) the Michael J. Fox Foundation, (2) Parkinson Association of Alberta, (3) Parkinson Canada, (4) Parkinson Society British Columbia, and (5) Parkinson Québec. Patient perspectives were obtained from surveys, phone interviews, and a guidebook published by the patient group. The following is a summary of key input from the perspective of the patient groups:

- The patient groups described PD as a heterogeneous condition that encompasses a large number of motor and non-motor symptoms experienced by each patient to different degrees, from mild to severe. Early-stage disease symptoms may affect a patient's ability to work, socialize, exercise, eat, sleep, and perform daily tasks or participate in recreational activities. Mid- and late-stage disease often involves speech impairment, hypophonia, swallowing problems, drooling, poor stomach emptying, flexed or bent posture, postural instability, rigidity in neck and trunk, motor fluctuations and dyskinesia that can progress into more severe walking problems, instability, shuffling, festination, and freezing of gait. PD psychosis or dementia can occur. Almost half of respondents felt their family and/or social relationships were negatively impacted by the disease and a large majority had experienced a loss in quality of life.
- The main and most-effective treatment for PD in mid- and late-stage disease is levodopa; however, its use is related to a higher risk of long-term side effects and motor complications. As PD progresses, the effectiveness of levodopa may decline: individual doses may fail to kick in, gradually wear off before the next dose is due, or stop working unexpectedly. This causes an OFF state in patients with PD that is associated with a much higher degree of disability and loss of confidence than the ON state.
- Medications that can provide relief during the troublesome or debilitating periods of the day are deemed important by patients who experience OFF episodes. Altering the dose or frequency of administration of levodopa during these times is not always possible or effective. Patients expressed a desire for additional medications with a quick onset that are available on demand, preferably oral administration, and with tolerable side effects.

Clinical Trials

The systematic review included one double-blind, placebo-controlled RCT (Study CTH-300, N = 109) of patients with PD.

This was a phase III, multi-centre trial that assessed the efficacy and safety of APO SL versus placebo in patients with PD over a 12-week period. Adult patients with idiopathic PD, with clinically meaningful response to levodopa therapy and with at least one OFF episode per day were included. The trial contained two phases. In the open-label dose titration phase, if the patient responded to single, escalating doses of APO (started with 10 mg and increased in 5 mg increments to a maximum dose of 35 mg) with a full ON response within 45 minutes of drug administration, that particular dose would be used in the next double-blind maintenance treatment phase. Any patients who reached 35 mg at the last titration visit and did not exhibit a full ON response within 45 minutes were terminated from the study. Patients who completed the dose titration phase entered the maintenance treatment phase and were randomly assigned to 12-week treatment with APO SL (n = 54) or placebo (n = 55). The average number of daily doses was 2.2

in the APO group and 2.5 in the placebo group. The primary efficacy end point was the mean change from pre-dose in the MDS-UPDRS III score at 30 minutes post-dose at the week 12 visit of the maintenance treatment phase. Other efficacy outcomes in CTH-300 included frequency of patient-rated 30-minute post-dose full ON response, change in PD symptoms, and HRQoL. The safety profile of APO was examined as well.

A hierarchical testing approach was used for the analyses of the primary and secondary efficacy end points to control the familywise type I error rate. Ten efficacy end points, including the primary and key secondary end points, were included in this procedure. Statistical significance was not achieved for the secondary efficacy end points ranked third (percentage of patients with a full ON response within 30 minutes post-dose that had a duration of at least 30 minutes at week 12) in the hierarchical testing; therefore, statistical significance cannot be formally claimed for any of the end points ranked after this end point. Another major limitation of CTH-300 was the substantial missing data in the trial, particularly in the APO arm (37%). Results of the sensitivity analyses for missing data handling supported the findings from the primary analysis. There was a lack of direct evidence regarding the comparative effectiveness and safety of APO SL relative to other active treatments in the study population.

A number of predefined subgroup analyses based on various patient baseline characteristics were conducted to examine the consistency of the primary analysis results across subgroup levels; however, none of these subgroups were included as a stratification variable at randomization.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following: change in mobility, assessment on ON/OFF states, symptom reduction, HRQoL, patient satisfaction, time to response, and safety.

- Mobility and/or hypomobility was measured with change from pre-dose to 30 minutes post-dose in the MDS-UPDRS III score at week 12. This was the primary outcome in CTH-300. MDS-UPDRS is a widely used tool to measure disease severity, progression, and treatment response in patients with PD. It consists of four parts. Part III of MDS-UPDRS (motor examination) comprises 18 items. Each item is rated on a scale of 0 to 4, with total score ranging from 0 (no disability) to 56 (highest disability). Minimal clinically important differences of –3.25 points for detecting minimal but clinically meaningful improvement and 4.63 points for observing minimal but clinically meaningful worsening were reported in a PD population including all disease severity levels.
- Assessment of ON/OFF states were presented as percentage of patients with a full ON response within 30 minutes post-dose at week 12 and percentage of patients with a full ON response within 30 minutes post-dose with a duration of 30 minutes or longer at week 12. These were secondary efficacy outcomes in CTH-300.
- Symptom reduction was measured with the Epworth Sleepiness Scale (ESS). The ESS is an instrument that examines a patient's sleepiness or ability to doze off during the day in eight situations. A total ESS score is obtained by summing the responses to the eight individual items, which yields a score between 0 and 24, with higher scores indicating more sleepiness associated with daily life. Change from baseline in total ESS score at week 12 was a secondary efficacy outcome in CTH-300.
- HRQoL was measured with the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the EuroQol 5-Dimensions (EQ-5D). The PDQ-39 is a commonly used, validated, self-administered, PD-specific HRQoL measure consisting of 39 items that measure eight domains of health. An overall summary index is created by averaging the eight domain scores, ranging from 0 to 100. Higher summary index scores indicate worse quality of life. EQ-5D was used to evaluate patient's general well-being. These were secondary efficacy outcomes in CTH-300.
- Patient satisfaction was measured using the Patient Global Impression of Improvement (PGI-I). This was a patient-rated instrument to evaluate their response to a therapy. Patient response was rated from 1 = "very much improved" to 7 = "very much worse." The percentage of patients improved (very much improved, much improved, or minimally improved) at week 12 was a secondary efficacy outcome in CTH-300.
- Time to response refers to the interval between drug administration and an observed effect. Patients were asked about their ON/OFF state at different timepoints post-dose at each study visit and were asked to report the time to when the study drug was starting to have an effect, if applicable. Time to response at week 12 was a secondary efficacy outcome in CTH-300.

Efficacy

At week 12, the mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS III score (primary end point) for the APO group (–11.1 points; standard deviation [SD] = 1.46) was statistically significantly lower compared with placebo (–3.5 points; SD = 1.29), and the least square mean treatment difference (APO minus placebo) was –7.6 points (95% CI, –11.5 to –3.7; P = 0.0002). This was considered a clinically significant change according to the clinical expert. In MDS-UPDRS, lower scores indicate less disability and better mobility.

Additional outcomes were measured as secondary end points, such as percentage of patients with a full ON response within 30 minutes at week 12, mean change from baseline to week 12 in PDQ-39 and PGI-I, and time to effect. Percentage of patients with a patient-rated full ON response within 30 minutes post-dose at week 12 was the key secondary end point in CTH-300. A statistically significant difference was observed in favour of APO versus placebo in the percentage of patients achieving a full ON response within 30 minutes post-drug administration at week 12 (predicted response rate: 35% for APO versus 16% for placebo; adjusted odds ratio 2.81; 95% CI, 1.04 to 7.64; P = 0.0426). The percentage of patients with a full ON response post-dose with a duration of at least 30 minutes at week 12 was 22% in the APO group and 15% in the placebo group; however, a statistically significant difference was not detected for this outcome (adjusted odds ratio = 2.80; 95% CI, 1.00 to 7.84; P = 0.0501). Between-group difference in change from baseline in the PDQ-39 summary index score at week 12 was not statistically significant (APO = 0.31 versus placebo = –1.67; mean difference = 1.98; 95% CI, –2.16 to 6.12; P = 0.34). Patients treated with APO (37%) were more likely to report “improved” than those treated with placebo (20%) at week 12 using the PGI-I instrument. The median time to when study medication started to have an effect at week 12 was 21 minutes for APO, while it was not estimable in the placebo group.

Change in sleepiness disorders measured with the ESS was numerically similar between APO and placebo. The change in the ESS summary score at week 12 was 0.5 and –0.6 for APO and placebo, respectively. Change in EQ-5D-5L health index score was –0.03 and 0 for APO and placebo, respectively. Note that change in ESS and EQ-5D-5L scores were not adjusted for multiplicity.

Harms (Safety)

In CTH-300, during the dose titration phase, the frequency of adverse events (AEs) was 58.2%. During the double-blind maintenance treatment phase, the frequency of AEs was higher (88.9%) in the APO group compared with the placebo (45.5%). The majority of the AEs were considered mild to moderate. The most common AEs reported with APO were gastrointestinal disorders (31.9% during dose titration phase; APO = 53.7% versus placebo = 10.9% during maintenance treatment phase), followed by nervous system disorders (26.2% during dose titration phase; APO = 31.5% versus placebo = 7.3% during maintenance treatment phase), respiratory, thoracic, and mediastinal disorders (APO = 22.2% versus placebo = 1.8% during maintenance phase), general disorders and administration site conditions (APO = 18.5% versus placebo = 7.3% during maintenance treatment phase), and psychiatric disorders (APO = 14.8% versus placebo = 3.6% during maintenance treatment phase).

Isolated cases of serious AEs were reported, one in the titration phase and three in the maintenance treatment phase (two [3.7%] with APO and one [1.8%] with placebo).

Patients treated with APO were more likely to withdraw treatment because of AEs (APO = 27.8% versus placebo = 7.3%) during maintenance treatment phase. One patient suffered a cardiac arrest and died while being treated with 15 mg APO during the maintenance treatment phase, and the death was considered possibly related to treatment by the investigator.

In terms of harms of particular interest, the occurrence of gastrointestinal disorders, application site reactions (such as stomatitis, oral ulcers, and oral irritation), allergic or sensitivity responses to the formulation, daytime sudden onset of sleep, falls and injuries, and hypotension were higher in APO-treated patients compared with placebo.

Indirect Treatment Comparisons

One sponsor-submitted indirect treatment comparison (ITC) was included, which was a systematic literature review (SLR) followed by a network meta-analysis (NMA) that compared the clinical efficacy and safety of APO SL with APO SC. The main inclusion criteria for studies in the search was adults (18 years or older) patients with PD who experience intermittent OFF episodes. The primary comparators for the SLR and subsequent NMA were sublingual and subcutaneous administrations of APO. A placebo intervention

was the only other comparator allowed for a study to be included in the SLR. Conclusions of clinical efficacy were based primarily on mean differences for measures of hypomobility in patients with PD, including MDS-UPDRS motor scores and UPDRS motor scores. The NMA was conducted using a Bayesian modelling approach, and both fixed- and random-effects models were used for analyses.

A total of eight RCTs met the inclusion criteria for the NMA. For the primary outcome of differences in UPDRS or MDS-UPDRS motor score at 20 to 30 minutes post-dose, the analysis showed a larger decrease in mean motor score for patients on APO SC compared with those on APO SL, with APO SL patients decreasing a minimum of 12.40 points on average (95% credible interval [CrI], 7.63 to 17.17). At 60 minutes from baseline, the results did not favour either treatment (mean difference = –0.52; 95% CrI, –8.01 to 6.98). At 90 minutes from baseline, a statistically significant mean difference was estimated in favour of APO SL (mean difference = –8.21; 95% CrI, –15.02 to –1.38).

The rates of AEs ranged from 32.5% to 88.9% for patients treated with APO SL, and from 70% to 85% for patients treated with APO SC. The authors concluded that the safety results could not be formally compared between APO SL and APO SC primarily due to study heterogeneity.

Key limitations to the ITC included a sparse network and study differences in design and patient characteristics. Neither of these comparisons provided compelling evidence to draw conclusions in regard to comparative efficacy and safety of APO SL to APO SC.

Cost and Cost-Effectiveness

APO SL (Kynmobi) is available as a 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg sublingual film, at a submitted price of $8.60 per film. The recommended dose is 10 mg to 30 mg daily with a maximum of five daily doses or 90 mg per day. The average total annual drug acquisition cost of APO SL is $6,278 per patient (based on an average dosing frequency of two films per day as per the product monograph), with a maximum cost of $15,695 per patient.

The sponsor submitted a cost-utility analysis based on a Markov state-transition model comparing APO SL versus APO SC (Movapo) as an adjunct to the standard of care (oral therapy for PD) for the acute, intermittent treatment of OFF episodes in adult patients with PD. The sponsor's economic model consisted of five health states: four health states are OFF health states based on quartiles of waking time spent in OFF state (i.e., 0% to 25%, 26% to 50%, and so on), and the remaining health state is death. Patients entered the model in one of the four OFF health states according to the initial distribution of mean baseline hours spent in OFF prior to treatment. Patients on APO SC and APO SL transitioned toward a less severe OFF state after the first six-month cycle and could only transition to progressively worse OFF states due to symptom progression or death thereafter. The change in total OFF time per day for APO SL was informed from the CTH-300 clinical trial, and APO SC was based on the sponsor-commissioned ITC. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon.

The following key limitations were identified:

- The comparative treatment effects of APO SL with APO SC are uncertain given the limitations of the clinical trial studies and the sponsor-submitted ITC as identified in the CADTH clinical review.
- The sponsor considered patient OFF progression in the economic model but did not include natural disease progression according to stage on Hoehn & Yahr scale. This assumes patients would not experience disease progression over the model time horizon.
- Uncertainty exists as to the long-term treatment effect of APO SL as the efficacy of treatments for PD tend to attenuate as the disease progresses. The sponsor did not explore the impact of the waning of treatment effects.
- The time horizon of five years was not sufficient given that PD is a progressive condition, and other interventions may be required as the patient's condition advances. Furthermore, the lack of inclusion of subsequent treatments, and the uncertainty regarding the timing and impact of subsequent treatments, increased the uncertainty in the cost-effectiveness of APO SL.

The CADTH base case reflected changes to the following parameters: assuming equal efficacy for APO SL and APO SC with respect to reduction in OFF hours per day and equal safety events.

The CADTH reanalysis indicates that when assuming similar clinical effects, APO SL is cost-saving compared with APO SC (savings of $3,695) over five years at the current submitted price. Based on the CADTH review of APO SC, a 65% price reduction was required to achieve an incremental cost-effectiveness ratio of $50,000 per quality-adjusted life-year gained. Where participating drug plans were able to negotiate this price reduction, a price reduction of 60% would be required for APO SL to be considered cost-saving. If APO SC does not represent current treatment for intermittent OFF episodes and standard of care (i.e., oral therapy for PD) is used, APO SL would not be considered cost-effective at the submitted price.

October 21, 2020 Meeting (Initial)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None.

Conflicts of Interest

None.

February 17, 2021 Meeting (Reconsideration)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None.

Conflicts of Interest

None.