CADTH

CADTH Common Drug Review

Pharmacoeconomic Report

Apomorphine Hydrochloride (Kynmobi)

(Sunovion Pharmaceuticals Canada Inc.)

Indication: The acute, intermittent treatment of “OFF” episodes in patients with Parkinson disease

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
APO SC	apomorphine hydrochloride subcutaneous
APO SL	apomorphine hydrochloride sublingual
H&Y	Hoehn & Yahr
ITC	indirect treatment comparison
LY	life-year
PD	Parkinson disease
QALY	quality-adjusted life-year
SoC	standard of care
WTP	willingness to pay

Executive Summary

The executive summary is made up of 2 tables, Table 1 (background) and Table 2 (economic evaluation), and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Apomorphine hydrochloride (Kynmobi), 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg sublingual film
Submitted price	Apomorphine hydrochloride, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg: $8.60 per sublingual film
Indication	The acute, intermittent treatment of OFF episodes in patients with Parkinson disease
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	June 12, 2020
Reimbursement request	As per indication
Sponsor	Sunovion Pharmaceuticals Canada Inc.
Submission history	Previously reviewed: Yes Indication: The acute, intermittent treatment of hypomobility, OFF episodes associated with Parkinson disease including end-of-dose wearing OFF (including early-morning OFF), partial, delayed, no ON, and unpredictable OFF. Recommendation date: Not applicable Recommendation: Withdrawn

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	• Cost-utility analysis • Markov model
Target population	Adult patients with PD who experience acute, intermittent OFF episodes.
Treatment	APO SL
Comparators	APO SC
Perspective	Canadian publicly funded health care payer.
Outcomes	QALYs, LYs
Time horizon	5 years
Key data source	Sponsor-submitted ITC reporting mean change in total OFF time. The ITC included 2 trials studying APO SL (CTH-300) and APO SC (APO-202).
Submitted results for base case	APO SL is dominant, i.e., more effective (increase of 0.003 QALYs) and less expensive (cost savings of $6,449) compared with APO SC.
Key limitations	CADTH identified the following key limitations:

Component	Description
	• The treatment effects of APO SL compared 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 H&Y stage. 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 5 years was not sufficient, given that PD is a progressive condition for which 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.
CADTH reanalysis results	• CADTH undertook reanalyses to address the identified limitations by: assuming equal efficacy for APO SL and APO SC with respect to reduction in OFF hours per day and equal safety events. • CADTH found that when assuming similar clinical effects, APO SL represents a cost saving compared with APO SC (savings of $3,695). • Based on CADTH's review of APO SC, a 65% price reduction would be required to achieve an ICER of $50,000 per QALY gained. Where participating drug plans are able to negotiate this price reduction, a price reduction of 60% would be required for APO SL to be a cost-saving option.

APO = apomorphine hydrochloride; H&Y = Hoehn & Yahr; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; PD = Parkinson disease; LY = life-year; QALY= quality-adjusted life-year; SC = subcutaneous; SL = sublingual.

Conclusions

CADTH undertook reanalyses to address uncertainty regarding the clinical benefits of apomorphine hydrochloride sublingual (APO SL) film. Aligned with the CADTH Clinical Review, given no differences in clinical efficacy or harms could be concluded, CADTH assumed: equal efficacy with respect to reduction in OFF hours per day, and equal rates of adverse events (AEs) and treatment discontinuation as a result of AEs.

In the CADTH reanalyses, at the submitted price, APO SL was less costly when compared with the list price of apomorphine hydrochloride subcutaneous (APO SC), representing savings of $3,695 per patient over 5 years.

Some uncertainties remain, as the model did not account for the need for subsequent or adjunctive treatments, treatment effect waning, or the natural disease progression of Parkinson disease (PD). When used as an adjunctive treatment for the management of PD, APO SL could represent a less expensive treatment option for the treatment of OFF episodes relative to APO SC; however, any price negotiations for APO SC would need to be considered for APO SL. There was further uncertainty with regard to the current usage of APO SC and whether it is reflective of current clinical management of OFF episodes.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Input was received from 5 patient groups: The Michael J. Fox Foundation, Parkinson Canada, the Parkinson Association of Alberta, Parkinson Society British Columbia, and Parkinson Québec. These groups noted that injectable apomorphine is a pharmaceutical option in Canada to provide relief for patients during OFF episodes; however, this medication was considered invasive with a limited window of opportunity for use and is associated with potential side effects. Patients cited an unmet need for new treatments that offer better symptom control and side effect management while providing a "grace period" during an OFF episode.

Generally, the patient groups responding to this call for input did not have experience with sublingual apomorphine, and mixed results were received regarding patient experience using injectable or pump apomorphine (results ranged from discontinuing treatment, to improved quality of life, to positively life changing). However, there is hope that sublingual delivery will be more convenient, more tolerable, and more effective than the injectable format.

Several of these concerns were addressed in the sponsor's model:

- Treatment efficacy (change in daily OFF status) was incorporated using results from the sponsor-submitted indirect treatment comparison (ITC).
- Quality of life was captured according to each health state (Hoehn & Yahr [H&Y] stage and time spent in an OFF state).
- AEs were included (costs and quality-of-life decrements).

In addition, CADTH addressed this concern:

- It was uncertain whether treatment discontinuation due to AEs would be clinically different between APO SC and APO SL; therefore, CADTH assumed equal treatment discontinuation rates.

However, this concern could not be addressed by CADTH:

- Disease progression according to H&Y stage was not adequately captured.

Economic Review

The current review is for APO SL (Kynmobi) for the treatment of acute, intermittent treatment of OFF episodes in adult patients with PD.[1]

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis based on a Markov state transition model comparing APO SL (Kynmobi) with APO SC (Movapo) as an adjunct to the standard of care (SoC) (oral therapy for PD) for the acute, intermittent treatment of OFF episodes in adult patients with PD.[2] The modelled population was consistent with the CTH-300 phase III clinical trial for APO SL and aligned with the funding request.[2,3]

The recommended therapeutic dose of APO SL is 10 mg to 30 mg administered sublingually as needed, with no more than 5 films administered per day.[4] Starting at the recommended dose of 10 mg, patients are titrated in 5 mg increments with APO SL to achieve optimal response and tolerability prior to maintenance, with a maximum dose of 30 mg. The comparators included APO SC (2 mg to 6 mg [0.2 mL to 0.6 mL] as needed, with a maximum daily dose of 20 mg [2 mL]).[5] At a price of $8.60 per sublingual film (regardless of strength), the average total annual drug acquisition cost for APO SL is $6,278 per patient, with a maximum cost of $15,695 per patient.

The clinical outcomes of interest were quality-adjusted life-years (QALYs) and life-years (LYs). The economic evaluation was undertaken over a 5-year time horizon using 6-month cycle lengths (half-cycle correction applied) from the perspective of the public health care payer. Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

A cohort-level Markov model was developed by the sponsor and consisted of 5 health states: 4 health states are OFF health states (OFF1, OFF2, OFF3, OFF4) based on quartiles of waking time spent in the OFF state (i.e., 0% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%), and the remaining health state is death. Patients entered the model in 1 of the 4 OFF health states according to the initial distribution of mean baseline hours spent in OFF prior to treatment (4.14 hours per day; standard deviation, 1.29 hours) as reported in CTH-300,[3] with the assumption that patients were awake for 16 hours per day. Patients on APO SC and APO SL transitioned toward a less severe OFF state after the first 6-month cycle, with the proportions in each state based on the reduction in time spent in the OFF state (Table 13). No further improvement in time spent in the OFF state occurred after the first cycle, and patients could transition to progressively worse OFF states only due to symptom progression or death. Data for symptom progression rates were obtained from Walter and Odin et al.[6] and are presented in Table 14. Patients may discontinue treatment due to lack of efficacy or AEs, which were assumed to occur over the first cycle only.

Model Inputs

The baseline characteristics in the model were aligned with those of the CTH-300 trial patient population, a phase III randomized, placebo-controlled trial in adult patients with PD.[3] The change in total OFF time per day was estimated by multiplying the mean number of

treated OFF episodes per day (2.20 episodes) from the clinical trial CTH-300[3] by the mean duration of OFF per episode with each treatment (45.18 minutes for APO SL and 40.80 minutes for APO SC), based on the sponsor-commissioned ITC. Patients who discontinued treatment were assumed to either receive no treatment or switch to the alternative apomorphine product if discontinuation was due to a local AE (i.e., oral AEs for APO SL and injection-site reactions for APO SC). Discontinuation rates were based on data from the CTH-300[3] and APO-202[7] clinical trials (Table 15). AE rates were based on the open-label safety studies, APO-401 and CTH-301.[8,9] Mortality was informed using Statistics Canada (2018)[10] life tables and adjusted based on the hazard ratio of death for patients with PD according to age (i.e., older than 65 years of age and younger than 65 years of age), as reported in Liou et al.[11] and on the proportion of patients in each H&Y stage.

Health state utility values for each of the OFF health states varied according to H&Y stage. These values were estimated from Lowin et al.[12] and are presented in Table 16. The proportions of patients in each H&Y stage in the CTH-300[3] clinical trial were used to calculate a weighted utility value for each OFF health state. Utility decrements for falls were applied for 1 year and were derived from a Swedish study on osteoporosis-related falls[13] (Table 17), whereas utility decrements for hypotension, administration-site reaction, dizziness, dyskinesia, somnolence, and hallucinations were applied for 2 weeks and were obtained from Walter and Odin.[6]

Costs included drug costs, health care resource utilization and monitoring, and AEs. The drug price for APO SL was obtained from the sponsor and the price for APO SC was based on the unit price of a pre-filled pen (must be used within 48 hours) from the Ontario Drug Benefit Formulary Exceptional Access Program.[14] Health care utilization was assumed to vary between OFF stages, with hospitalization, specialist visits, and general practitioner visits based on a previous CADTH submission of Movapo,[15] which was informed by Findley et al.[16] Computed tomography (CT) scans were assumed to have the same frequency as hospitalizations (Table 18). It was assumed that AEs would consist of a specialist visit and would be resolved within the first treatment cycle, and that 10% of patients experiencing a fall would require hospitalization. Hospitalization costs were obtained from the Ontario Case Costing Initiative,[17] and physician visit and CT scan costs were taken from the Ontario Schedule of Benefits for Physician Services.[18] Costs were reported in 2020 Canadian dollars.

Summary of Sponsor's Economic Evaluation Results

The sponsor presented probabilistic analyses (1,000 iterations for the base-case and scenario analyses).

Base-Case Results

In the sponsor's base-case analysis, APO SL was less expensive (incremental savings, $6,449) and more effective (incremental QALYs, 0.003) than APO SC, resulting in APO SL being dominant in 80% of iterations (Table 3). At a willingness-to-pay (WTP) threshold of $50,000 per QALY, the probability of APO SL being cost-effective compared with APO SC was reported to be 94%.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental cost ($)	Total QALYs	Incremental QALYs	ICER ($ per QALY) versus APO SC
APO SC	89,559	–	3.078	–	–
APO SL	83,110	−6,449	3.081	0.003	Dominates APO SC

APO = apomorphine hydrochloride; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; SL = sublingual.

Note: The submitted analysis is based on publicly available prices of the comparator treatments. "Dominates" refers to the intervention being less expensive and more effective than the comparator.

Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor conducted probabilistic scenario analyses varying the discount rate, time horizon, half-cycle correction, discontinuation rates, response duration, treatment switching, efficacy and safety differences, AEs, disease progression, health state costs, and utility values.

APO SL remained a dominant strategy compared with APO SC in all scenarios, except when the duration of response to APO SL from maintenance visit 4 was utilized. In that case, APO SL is both less costly (cost savings of $5,303) and less effective (0.005 fewer QALYs) compared with APO SC.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations of the sponsor's analysis that have notable implications for the economic analysis:

- Uncertainty in comparative treatment effectiveness and safety: There is a lack of head-to-head randomized studies comparing APO SL with APO SC. Relative treatment efficacy was informed by an unpublished ITC conducted by the sponsor; however, these estimates may not be reliable, given the limitations identified by the CADTH clinical reviewers. In particular, the sponsor used trial data from CTH-300 and APO-202 to estimate the duration of OFF response. There are significant differences in study design, such as variation in trial duration and efficacy end points, as well as important limitations associated with the APO-202 study, which included its small sample size and potential for unblinding of patient and outcome assessors to treatment allocation.[19] Moreover, change in OFF time for APO SC was based on patient diary data, whereas change in OFF time for APO SL was inferred from the CTH-300 data, as no direct data were available. The fact that key model parameters were based on different data sources and study designs could introduce significant uncertainty into the analysis. Furthermore, the indirect estimate of the duration of OFF for the APO SC studies is likely biased in favour of APO SC (see CADTH Clinical Review for Kynmobi). Finally, as noted by the sponsor, since both therapies have an identical active ingredient, they are expected to provide similar efficacy. It was also noted that the ITC estimates for AEs were not presented by the sponsor due to limited reliability and interpretability.
    - In line with the aforementioned, and as per the feedback from the clinical expert consulted for this review, CADTH assumed equal efficacy with respect to the reduction in OFF hours per day, AE-related treatment discontinuation, and AE rates as part of the base-case reanalyses. As such, the CADTH base case focuses on a comparison of costs for APO SL and APO SC.

- While CADTH assumed equal rates of AEs in the CADTH base case, different rates of AEs and treatment discontinuation were explored in the scenario analyses.

- **Natural disease progression not adequately captured:** The sponsor incorporated patient OFF progression in the economic model; however, natural disease progression according to H&Y stage was not included as part of the analyses. This assumes patients would not experience disease progression over the model time horizon. Transition probabilities according to H&Y stage were utilized in previously published economic evaluations in PD (e.g., Kalabina et al.[20] and Lowin et al.,[12] which were derived from Palmer et al.)[21] to inform disease progression. Further, health state utilities according to both H&Y stage and OFF status were available. Given the availability of transition probabilities according to H&Y stages and health state utilities according to H&Y stage and OFF status, a model that captures PD and not just OFF episodes would have been informative to the assessment of APO SL to capture the time until the need for other treatment options and potential treatment waning as a result of disease progression. Based on the structural limitations of the sponsor's model, the impact on cost-effectiveness results is unknown.
  - Due to structural limitations, CADTH was unable to explore the impact of natural disease progression according to H&Y stages.
- **Potential treatment effect waning not considered**: Treatments for PD tend to lose efficacy as the disease progresses.[22] The clinical expert consulted by CADTH noted that patients who have progressed to more severe H&Y stages (stage 4 and 5) would benefit less from APO SL, as they would be more likely to have a decreased response to dopamine and therefore could require more intrusive therapies (e.g., deep-brain stimulation or levodopa plus carbidopa intestinal gel). This could result in an increase in the number of daily OFF episodes, subsequently increasing the number of APO SL administrations required.
  - As stated previously, the model did not consider the natural progression of PD and, due to structural limitations, CADTH was unable to explore the impact of treatment effect waning.
- **Subsequent treatment not adequately captured**: The clinical expert consulted by CADTH noted that the use of intermittent apomorphine may potentially delay the need for more invasive therapies, such as deep-brain stimulation or levodopa plus carbidopa intestinal gel for some patients. As the sponsor's model does not account for the impact of treatment on subsequent therapies, it was not possible to estimate any benefit, harm, quality of life, or cost differences that might occur between the 2 forms of apomorphine.
  - Due to structural limitations, CADTH was unable to explore the impact of subsequent treatment.
- **Short time horizon**: The sponsor's choice of a 5-year time horizon does not adequately reflect the downstream impacts of apomorphine use, given that patients are likely to transition to more advanced therapies (deep-brain stimulation, levodopa plus carbidopa intestinal gel) as the disease progresses. Furthermore, other published economic analyses of PD treatments have used a longer time horizon. The lack of inclusion of subsequent treatments, and their timing and impact, increased the uncertainty in the cost-effectiveness of APO SL.
  - A 5-year time horizon was used in the CADTH base case, as it is unlikely that downstream differences exist between APO SL and APO SC under the CADTH

base-case assumption of equal efficacy. Given the identified limitations with the sponsor's model, that is, not capturing progression of PD, the time horizon could not be adequately addressed in the reanalyses.

- **Appropriateness of comparator**: APO SC is currently listed on the majority of public drug program formularies (with the exception of Prince Edward Island); however, the clinical expert consulted by CADTH highlighted that there is currently a limited uptake for apomorphine treatments. This is mainly due to the availability of other adjunctive treatments, where treatment could be optimized to minimize OFF episodes, and the potential difficulty of administering subcutaneous treatments. Additionally, the clinical expert indicated the introduction of APO SL would further limit APO SC usage; therefore, the relevance of APO SC as a relevant comparator is uncertain. The sponsor did not consider SoC (i.e., oral therapy for PD) as a comparator.
    - CADTH considered SoC as a comparator in a scenario analysis using the clinical information from CTH-300. AEs and discontinuations due to AEs for SoC were reflective of the results for the placebo group and it was assumed patients would not switch treatment due to local site reactions. Given that efficacy inputs for APO SL represent a relative increase versus placebo, SoC was assumed to have no improvement in daily ON status. Costs for levodopa, with or without stable adjunctive therapies, were implicitly captured in the model, as costs would be equal for both treatments; therefore, no additional costs were applied for SoC.

Additional limitations were identified, but were not considered to be key limitations:

- **Uncertainty in treatment discontinuation rate during titration**: The sponsor indicated that Sunovion Pharmaceuticals Canada intends to provide APO SL samples in all strengths to physicians specializing in the diagnosis and treatment of patients with PD during the titration phase at no charge.[2] Therefore, the sponsor excluded discontinuations during the titration phase from the model, since patients who discontinue during titration would not incur any drug costs. However, discontinuation rates are used to inform the proportion of patients receiving each treatment in the first cycle. It is therefore inappropriate to exclude these rates from the model, since outcomes experienced by patients who discontinue during titration need to be accounted for. Further, no formal distribution plan was provided by the sponsor, and it is uncertain whether any access restrictions for this drug will impact this assumption.
    - Given the significant limitations associated with the APO-212 study, the limited available comparative information, and CADTH's assumption of equal efficacy and safety between APO SL and APO SC, CADTH maintained the sponsor's approach of excluding discontinuation rates during titration.
    - Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Statistics Canada life tables multiplied by a weighted HR for death due to PD derived from Liou et al. (2009)[11] and the proportion of patients in each H&Y stage in CTH-300.[3]	Unlikely to be appropriate. Taiwanese patients are unlikely to reflect the relative life expectancy of patients in Canada. Statistics Canada life tables already include Parkinson patients but, given the low prevalence of PD among those older than 45 years (0.0% to 2.0%),[23] double counting is unlikely to have an impact on results. No other publications assessing PD-specific mortality for the Canadian population were identified. CADTH removed adjusted mortality rates as part of the scenario analyses.
AE rates were based on open-label safety studies and were assumed to occur in cycle 1 only. Utility decrements for falls were applied for 1 year, whereas decrements for hypotension, administration-site reaction, dizziness, dyskinesia, somnolence, and hallucinations were applied for 2 weeks.	Acceptable, based on feedback from the clinical expert.
Only patients who discontinue treatment due to local AEs will switch between APO SC and APO SL.	Appropriate, based on feedback from the clinical expert.

AE = adverse event; APO = apomorphine hydrochloride; HR = hazard ratio; PD = Parkinson disease; SC = subcutaneous; SL = sublingual; H&Y = Hoehn & Yahr.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH reanalyses addressed several limitations within the economic model and are summarized in Table 5. CADTH was unable to address the lack of evidence on the long-term effectiveness of APO SL. Due to structural limitations, CADTH was unable to address the inclusion of subsequent treatment, treatment effect waning, or application of natural disease progression.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None.		
Changes to derive the CADTH base case		
1. Treatment efficacy: Assume equal efficacy with respect to the reduction in OFF hours per day	APO SC: 0.68 hours APO SL: 0.75 hours	APO SC: 0.75 hours APO SL: 0.75 hours
2. Treatment safety: Assume equal AE-related discontinuation, local site discontinuation, and AE rates	**AE-related discontinuation** APO SL: 14.8% APO SC: 5% Differential AE rates and local site discontinuation	**AE-related discontinuation** APO SL: 14.8% APO SC: 14.8% Equal AE rates and local site discontinuation
CADTH base case	–	Reanalysis 1 to 2

AE = adverse event; APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

CADTH's base-case results are presented in Table 6. Additional reanalyses and results are presented in Table 19.

In CADTH's base case, APO SL is the least costly option ($83,042) and provides 3.092 QALYs over a 5-year time horizon (Table 6). Based on APO SL having both equivalent efficacy and safety, the resulting CADTH base case reflected a cost-minimization approach where APO SL was less costly compared with APO SC and provided incremental cost savings of $3,695 (Table 7).

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case	APO SC	89,559	3.078	–
	APO SL	83,110	3.081	Dominates APO SC
CADTH reanalysis 1: Equal efficacy	APO SC	89,149	3.090	–
	APO SL	83,046	3.092	Dominates APO SC
CADTH reanalysis 2: Equal AE rates	APO SC	87,027	3.090	–
	APO SL	83,055	3.092	Dominates APO SC
CADTH base case: Reanalyses 1 to 2	APO SC	86,737	3.092	–
	APO SL	83,042	3.092	APO SL is cost saving

AE = adverse event; APO = apomorphine hydrochloride; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; SL = sublingual.

Note: The submitted analysis is based on publicly available prices for the comparator treatments.

Table 7: CADTH Reanalysis — Cost Breakdown

Discounted costs ($)	APO SL	APO SC	Difference ($) (for APO SL)
Total	**83,042**	**86,737**	**−3,695**
By health state			
OFF1	20,764	20,768	−4
OFF2	22,700	22,697	3
OFF3	8,851	8,848	3
OFF4	945	944	1
Treatment	29,685	33,383	−3,698
End of life	0	0	0
Adverse events	94	94	0
Domperidone	3	3	0

APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

Note: The submitted analysis is based on publicly available prices for the comparator treatments.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case to investigate the impact of including differential safety rates, treatment discontinuation, time horizon, applying minimum and maximum APO SL dosing, and removal of adjusted mortality (Table 8). An additional analysis was conducted to explore the cost-effectiveness of APO SL relative to SoC, given the limited uptake of APO SC.

Table 8: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario analyses		
1. Application of AEs	Equal AEs for both APO SL and APO SC	Differential AEs for both APO SL and APO SC
2. Equal treatment discontinuation	APO SC: 5% APO SL: 14.8%	APO SC: 5% APO SL: 5%
3. Removal of treatment discontinuation	APO SC: 5% APO SL: 14.8%	APO SC: 0% APO SL: 0%
4. Number of APO SL administrations per day (low)	2.20	1.00
5. Number of APO SL administrations per day (high)	2.20	5.00
6. Removal of adjusted mortality	Included	Excluded
7. Relevant comparator	APO SC	SoC

AE = adverse event; APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual; SoC = standard of care.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Based on the CADTH scenario analyses, the number of APO SL administrations (maximum 5 doses) had the largest impact on APO SL results, making APO SL more costly compared with APO SC (Table 20). In all other scenarios, APO SL was less costly than APO SC.

If APO SC is not considered an appropriate comparator, CADTH noted that APO SL has an incremental cost-effectiveness ratio of $602,089 per QALY when compared with SoC. At a WTP threshold of $50,000 per QALY, a price reduction of approximately 75% is required. It should be noted that differences exist between the CADTH review of Movapo and the current submission, mainly the use of updated health state utilities and costs; therefore, cost-effectiveness results and an associated price reduction should be considered within this context.

Price Reduction Analyses

Price reduction analyses were undertaken based on the CADTH base case by varying the price of both APO SL and APO SC, given the uncertainty regarding the negotiated price for APO SC. When considering the price reductions recommended in the CADTH Canadian Drug Expert Committee (CDEC) Recommendation report for APO SC (Movapo),[24] a cost of $21.48 per pen (a 50% reduction to achieve a WTP threshold of $100,000 per QALY) and $15.03 per pen (a 65% reduction to achieve a WTP threshold of $50,000 per QALY), the price of APO SL would need to be reduced by 45% and 60%, respectively, to result in similar in total costs (Table 9).

Table 9: CADTH Price Reduction Analyses — APO SL Versus APO SC (Multi-Way Analyses)

Price of APO SL	Price of APO SC				
	No reduction	50% reduction	55% reduction	60% reduction	65% reduction
Submitted	**APO SL is a cost saving ($3,695)**	APO SC is a cost saving ($11,761)	APO SC is a cost saving ($13,306)	APO SC is a cost saving ($14,852)	APO SC is a cost saving ($16,397)
45% reduction	**APO SL is a cost saving ($15,941)**	**APO SL is a cost saving ($486)**	APO SC is a cost saving ($1,060)	APO SC is a cost saving ($2,606)	APO SC is a cost saving ($4,151)
50% reduction	**APO SL is a cost saving ($17,302)**	**APO SL is a cost saving ($1,846)**	**APO SL is a cost saving ($301)**	APO SC is a cost saving ($1,245)	APO SC is a cost saving ($2,790)
55% reduction	**APO SL is a cost saving ($18,663)**	**APO SL is a cost saving ($3,207)**	**APO SL is a cost saving ($1,661)**	**APO SL is a cost saving ($116)**	APO SC is a cost saving ($1,430)
60% reduction	**APO SL is a cost saving ($20,023)**	**APO SL is a cost saving ($4,568)**	**APO SL is a cost saving ($3,022)**	**APO SL is a cost saving ($1,476)**	**APO SL is a cost saving ($69)**
65% reduction	**APO SL is a cost saving ($21,384)**	**APO SL is a cost saving ($5,928)**	**APO SL is a cost saving ($4,383)**	**APO SL is a cost saving ($2,837)**	**APO SL is a cost saving ($1,292)**

APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

Note: The submitted analysis is based on publicly available prices for the comparator treatments. Price reduction thresholds are based on the Canadian Drug Expert Committee Recommendation for APO SC to be considered cost-effective at $100,000 (50% reduction) and $50,000 (65% reduction) per QALY willingness-to-pay threshold.

Issues for Consideration

- **Other dosage forms for comparator:** Based on the product monograph, APO SC is also supplied as 2 mL ampoules. The price of the ampoules is unknown, as they are not currently marketed in Canada; however, should this change, the cost-effectiveness of APO SL compared with 2 mL ampoules of APO SC may differ from that of the 3 mL pre-filled pens.
- **Mode of administration:** Sublingual films may be easier to use than pre-filled multi-dose pens for injection, in particular for patients in the midst of an OFF period who may require the assistance of a caregiver to inject medication, which may not be an option for all patients. The clinical expert consulted by CADTH noted that since patients may be less likely to try an injection versus sublingual therapy, injectable apomorphine may be less commonly used in clinical practice. As such, there may be a greater demand with the availability of the sublingual form, which could impact budgets more than anticipated.

Overall Conclusions

CADTH undertook reanalyses to address the uncertainty regarding the clinical benefit of APO SL compared with APO SC by assuming equal efficacy with respect to reduction in OFF hours per day, and equal AE discontinuation and safety rates.

In the CADTH reanalyses, at the submitted price, APO SL was less costly (savings of $3,695 over 5 years) when compared with APO SC. Given the past CADTH recommendation for a price reduction for APO SC, should a 65% price reduction for APO

SC (to achieve a WTP threshold of $50,000 per QALY) be realized, the price of APO SL would need to be reduced by 60% to result in similar total costs.

Some uncertainties remain, as the model did not account for the need for subsequent or adjunctive treatments, treatment waning, or the natural disease progression of PD. APO SL could represent a less expensive treatment option for the treatment of OFF episodes relative to APO SC; therefore, any price negotiations for APO SC would need to be considered for APO SL. Where APO SC does not represent current treatment for intermittent OFF episodes and SoC (i.e., oral therapy for PD) is used, APO SL is not considered cost-effective at the submitted price.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from the clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table; therefore, the table may not represent the actual costs to public drug plans.

Table 10: CADTH Cost Comparison Table for Parkinson Disease — Intermittent OFF

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Apomorphine hydrochloride sublingual (Kynmobi)	**10 mg 15 mg 20 mg 25 mg 30 mg**	**Sublingual film**	**8.6000[a]**	**10 mg to 30 mg per episode, maximum 5 daily doses (90 mg per day)**	**17.20[a] Maximum: 43.00**	**6,278 Maximum: 15,695**
Apomorphine hydrochloride subcutaneous (Movapo)[b]	10 mg/mL	3 mL pen	42.9520 per pen[c]	0.2 mL to 0.6 mL per OFF episode, maximum 2 mL daily[c]	21.48 Maximum: 28.63	7,839 Maximum: 10,452

Note: Prices do not include dispensing fees. Annual cost calculations are based on 365 days per year.

The clinical expert consulted by CADTH noted that in the absence of apomorphine hydrochloride or other medication being available specifically for reducing OFF episodes, patients experiencing substantial OFF periods may have their levodopa plus carbidopa divided into more frequent doses or their dose of adjunctive therapies increased, or both. Patients with more advanced Parkinson disease are considered for deep-brain stimulation or levodopa plus carbidopa intestinal gel.

[a] Sponsor-submitted price;[2] the average frequency of dosing was 2 times per day, as per the sponsor's product monograph.[4]

[b] The sponsor's product monograph indicates that subcutaneous apomorphine is also supplied as ampoules; however, this form was not included as part of the submission.[5]

[c] Drug costs obtained from the Ontario Exceptional Access Program (accessed July 27, 2020);[26] prices assume at least 1 dose required every 48 hours and excess medication disposed of after that period.[5]

Table 11: CADTH Cost Comparison Table for Parkinson Disease — Adjunctive to Levodopa Therapy

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Current therapies used in moderate to advanced Parkinson disease						
Dopamine agonists						
Bromocriptine (generics)	2.5 mg 5 mg	Tablet Capsule	1.0188 1.5251	2.5 to 40 mg daily, in 2 to 3 doses[a]	1.01 to 12.20	372 to 4,453
Pramipexole (generics)	0.25 mg 0.50 mg 1 mg 1.5 mg	Tablet	0.1950 0.4018[b] 0.3901 0.3901	1.5 mg to 4.5 mg in 3 equal doses[a]	1.17	427
Ropinirole (generics)	0.25 mg 1 mg 2 mg 5 mg	Tablet	0.0710 0.2838 0.3122 0.8596	3 mg to 24 mg in 3 equal doses[a]	0.85 to 3.75	311 to 1,367
Rotigotine (Neupro)	2 mg per 24 hours 4 mg per 24 hours 6 mg per 24 hours 8 mg per 24 hours	Patch	3.5400 6.5000 7.2700 7.2700	2 mg to 16 mg daily	3.54 to 14.54	1,292 to 5,307

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Oral and gel levodopa plus decarboxylase inhibitor combinations						
Levodopa/ benserazide (Prolopa)	50 mg/12.5 mg 100 mg/25 mg 200 mg + 50 mg	Capsule	0.3197 0.5265 0.8839	1,000 mg to 1,200 mg of levodopa daily in 5 to 6 doses[b]	4.42 to 5.30	1,613 to 1,936
Levodopa/ carbidopa (generics)	100 mg/10 mg 100 mg/25 mg 250 mg/25 mg	Tablet	0.1479 0.2209 0.2466	300 mg to 1,500 mg of levodopa in 3 to 4 daily doses	0.66 to 1.48	242 to 540
	100 mg/25 mg 200 mg/50 mg	Controlled release tablet	0.3857 0.7115	200 mg to 1,600 mg of levodopa in 2 to 4 daily doses	0.71 to 5.69	260 to 2,078
Levodopa/ carbidopa (Duodopa)	20 mg/mL 5 mg/mL	100 mL gel	168.81[b]	20 mg to 200 mg levodopa per hour over a 16-hour period[a]	168.81 to 337.62	61,616 to 123,231
COMT inhibitors						
Entacapone (generics)	200 mg	Tablet	0.4010	200 mg to 1,600 mg daily in multiple doses	0.40 to 3.21	146 to 1,171
Levodopa/ carbidopa/ entacapone (Stalevo)	50 mg/12.5 mg/200 mg 75 mg/18.75 mg/200 mg 100 mg/25 mg/200 mg 125 mg/31.25 mg/200 mg 150 mg/37.5 mg/200 mg	Tablet	1.7471	600 mg to 1,600 mg of entacapone daily in multiple doses	5.24 to 13.98	1,913 to 5,102
MAO-B inhibitors						
Rasagiline (Azilect)	0.5 mg 1 mg	Tab	6.1285 6.1285	0.5 to 1 mg daily	6.13	2,237
Selegiline (generics)	5 mg	Tab	0.5021	5 mg twice daily	1.00	367
Other						
Amantadine (generics)	100 mg	Cap	0.5252	100 mg once or twice daily	0.53 to 1.05	192 to 383

COMT = catechol O-methyltransferase; MAO-B = monoamine oxidase B; SC = subcutaneous; SL = sublingual.

All prices are from the Ontario Drug Benefit Formulary (accessed July 2020)[25] unless otherwise indicated and do not include dispensing fees. Annual cost calculations based on 365 days per year.

[a] Represents the recommended maintenance dose, per the sponsor's product monograph.

[b] Saskatchewan formulary (accessed July 2020).[27]

Appendix 2: Submission Quality

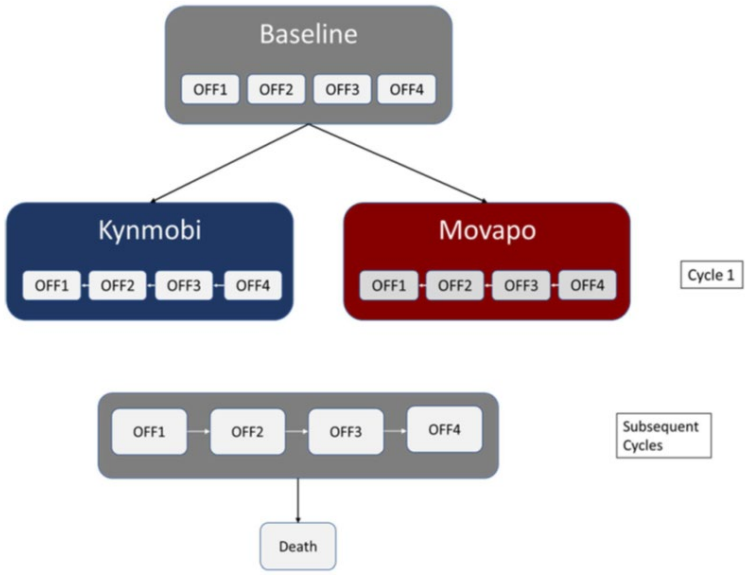
Table 12: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	NA
Model has been adequately programmed and has sufficient face validity	☒	☐	NA
Model structure is adequate for decision problem	☒	☐	NA
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	NA
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	NA
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	NA

NA = not applicable.

Appendix 3: Detailed Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[2]

Detailed Results of the Sponsor's Base Case

Table 13: Distribution of Patients by Health State

Health state	Baseline	APO SL cycle 1	APO SC cycle 1
OFF1 (0% to 25% waking time in OFF state)	48.5%	87.0%	86.5%
OFF2 (26% to 50% waking time in OFF state)	51.2%	12.9%	13.5%
OFF3 (51% to 75% waking time in OFF state)	0.4%	0.1%	0.1%
OFF4 (76% to 100% waking time in OFF state)	0.0%	0.0%	0.0%

APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 14: Health State Transition Probabilities After Cycle 1

Health state transition	Probability per 6 months
OFF1 to OFF2	0.127
OFF2 to OFF3	0.074
OFF3 to OFF4	0.043

Source: Sponsor's pharmacoeconomic submission.[2]

Table 15: Discontinuation and Treatment Switching Inputs Used in the Model

	Titration phase discontinuation (%)	Active phase discontinuation (%)	Proportion of discontinued patients switching to alternative product (%)	Proportion of discontinued patients not receiving further treatment (%)
APO SL	16.3	14.8	25.0	75.0
APO SC	5.0	5.0	3.75	96.25

APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Table 16: Health State Utility Values

Health state	Hoehn & Yahr stage					Weighted utility used in the model
	1	2	3	4	5	
OFF1	0.79	0.68	0.57	0.46	0.35	0.67
OFF2	0.76	0.65	0.54	0.43	0.32	0.64
OFF3	0.73	0.62	0.51	0.40	0.29	0.60
OFF4	0.70	0.59	0.48	0.37	0.26	0.57

Source: Sponsor's pharmacoeconomic submission.[2]

Table 17: Costs and Utility Decrement of Adverse Events

Adverse event	Percentage of patients experiencing an AE		Resource use	Duration of AE	Utility decrement	Total cost per patient ($)	
	APO SL	APO SC				APO SL	APO SC
Fall	7.0%	33.0%	Assumed 10% of patients experience a hospitalization	One year	−0.5%	108.65	512.19
Hypotension or syncope	0.6%	2.4%	One specialist visit	Two weeks	−0.01	0.95	3.78
Injection- or oral-site reaction	34.5%	15.0%	One specialist visit	Two weeks	0.00	54.82	23.84
Dizziness	6.4%	22.0%	One specialist visit	Two weeks	−0.01	10.17	34.96
Dyskinesia	5.5%	24.0%	One specialist visit	Two weeks	−2.5%	8.74	38.14
Somnolence	6.4%	21.0%	One specialist visit	Two weeks	0.00	10.17	33.37
Hallucinations	2.3%	19.0%	Two specialist visits	Two weeks	0.00	7.31	60.38

AE = adverse event; APO = apomorphine hydrochloride; SC = subcutaneous; SL = sublingual.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Table 18: Health Care Resource Use and Unit Costs Applied by OFF State

Resource	Frequency Per 6 months				Unit cost ($)	Source for unit cost
	OFF1	OFF2	OFF3	OFF4		
Hospitalization	0.26	0.36	0.60	0.60	15,521	OCCI CMG Grouper: 023, 2010/2011[17]
Specialist visits	1.45	1.41	1.40	1.40	158.11	Ontario SoB,[18] average of A185, A180, A186,A183,A184, C185, C180, C186
GP visits	1.59	1.98	1.95	1.95	61.55	Ontario SoB,[18] average of A005, A006
MRI	0.00	0.00	0.00	0.00	83.05	Ontario SoB,[18] average X421, E875
CT	0.26	0.36	0.60	0.60	61.35	Ontario SoB,[18] average X400, X401, X188

CMG = case mix group; CT = computed tomography; GP = general practitioner; OCCI = Ontario Case Costing Initiative; SoB = Schedule of Benefits.

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: CADTH Detailed Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 19: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	APO SL	APO SC	Incremental
Discounted LYs			
Total	4.776	4.776	0.000
OFF1	2.366	2.366	0.000
OFF2	1.904	1.904	0.000
OFF3	0.456	0.456	0.000
OFF4	0.049	0.022	0.000
Discounted QALYs			
Total	3.092	3.092	0.000
OFF1	1.577	1.577	0.000
OFF2	1.212	1.212	0.000
OFF3	0.276	0.276	0.000
OFF4	0.028	0.028	0.000
Discounted costs ($)			
Total	83,042	86,737	−3,695
By health state			
OFF1	20,764	20,768	−4
OFF2	22,700	22,697	3
OFF3	8,851	8,848	3
OFF4	945	944	1
Treatment	29,685	33,383	−3,698
End of life	0	0	0
Adverse events	94	94	0
Domperidone	3	3	0
ICER ($ per QALY)	**APO SL is cost saving**		

APO = apomorphine hydrochloride; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SC = subcutaneous; SL = sublingual.

Scenario Analyses

Table 20: CADTH Scenario Analyses Results

Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Scenario 1: Application of AEs			
APO SC	86,956	3.087	–
APO SL	83,046	3.090	Dominates APO SC
Scenario 2: Equal treatment discontinuation			
APO SC	89,184	3.092	–
APO SL	84,984	3.092	APO SL is less costly ($4,200 cost savings)
Scenario 3: Removal of treatment discontinuation			
APO SC	90,451	3.093	–
APO SL	85,986	3.093	APO SL is less costly ($4,465 cost savings)
Scenario 4: Number of APO SL administrations per day (low)			
APO SC	88,568	3.072	–
APO SL	70,042	3.072	APO SL is less costly ($18,526 cost savings)
Scenario 5: Number of APO SL administrations per day (high)			
APO SC	86,395	3.104	–
APO SL	117,348	3.104	APO SC is less costly ($30,953 cost savings)
Scenario 6: Removal of adjusted mortality			
APO SC	90,193	3.211	–
APO SL	86,369	3.211	APO SL is less costly ($3,825 cost savings)
Scenario 7: SoC as comparator			
SoC	58,730	3.051	–
APO SL	81,868	3.089	602,089 versus SoC

AE = adverse event; APO = apomorphine hydrochloride; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; SL = sublingual; SoC = standard of care.

Note: “Dominates” refers to the intervention being less expensive and more effective than the comparator.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Table 21: Summary of Key Takeaways

Key takeaways of the budget impact analysis

• CADTH identified the following key limitations of the sponsor's analysis:
  ○ The market size was underestimated, as the sponsor included only patients 40 years of age or older. Patients with early onset Parkinson (i.e., younger than 40 years of age) were excluded; however, given that these patients represent a small proportion of the target population (0.8%), the impact on results is minimal.
  ○ Treatment titration was not included in the model; however, results are likely biased against APO SL.
• CADTH reanalyses included: incorporating patients with early onset Parkinson and the proportion of patients receiving levodopa/carbidopa.
• Based on the CADTH reanalyses, the budget impact is expected to be $1,618,459 in year 1, $4,010,565 in year 2, and $6,200,845 in year 3, with a 3-year budget impact of $11,829,869.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis assessed the introduction of APO SL as an adjunct to SoC for the acute, intermittent treatment of OFF episodes in adult patients with PD. The budget impact analysis was undertaken from the national public payer perspective for the Canadian setting over a 3-year time horizon (2021 to 2023) using a prevalence-based approach. An overview of the sponsor estimation of the eligible population size can be found in Figure 2. The sponsor included drug acquisition costs but excluded drug price adjustments (i.e., deductibles, markups, co-payments, dispensing fees, and premiums). Key inputs to the budget impact analysis are documented in Table 22.

Figure 2: Sponsor's Estimation of the Eligible Population Size

PD = Parkinson disease.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 22: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Target population	
Number of parkinsonism patients aged ≥ 40 years (year 1/year 2/year 3)	89,360/ 92,498/ 95,747[28]
Proportion of parkinsonism patients diagnosed with PD	80%[29]
Percentage of patients with PD treated with levodopa/carbidopa	[redacted]%[a]
Percent of patients with PD optimized on therapy	[redacted]%[a]
Percent of patients with PD optimized on PD therapy experiencing OFF episodes	[redacted]%[a]
Percentage of eligible patients covered by public payer	91.38%[23,30]
Number of patients eligible for new drug (year 1 / year 2 / year 3)	[redacted]
Market uptake (3 years)	
Uptake (reference scenario)	
BSC	[redacted]
APO SC	[redacted]
Uptake (new drug scenario)	
BSC	[redacted]
APO SC	[redacted]
APO SL	[redacted]
Cost of treatment (per patient)	
Annual costs	
APO SC	$7,839
APO SL	$6,906

APO = apomorphine hydrochloride; BSC = best supportive care; PD = Parkinson disease; SC = subcutaneous; SL = sublingual.

Note: Sponsor assumes market size growth of 50% in year 1 for the new drug scenario for patients receiving intermittent treatment of OFF episodes due to the introduction of a sublingual formulation of apomorphine. APO SL is assumed to capture 80% of market share from APO SC.

[a] Opinion of the sponsor's clinical expert.

Source: Sponsor's pharmacoeconomic submission.[2]

Summary of Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case revealed that the incremental expenditures associated with the reimbursement APO SL for the acute, intermittent treatment of OFF episodes in patients with PD are expected to be $[redacted] in year 1, $[redacted] in year 2, and $[redacted] in year 3. The total 3-year budget impact for reimbursing APO SL was estimated to be $[redacted](

Table 25).

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations of the sponsor's analysis that have notable implications on the results of the budget impact analysis:

- **Market size underestimated:** Based on available data, the sponsor included only patients 40 years or older who were diagnosed with parkinsonism; however, a small subset of patients will be diagnosed prior to 40 years of age (i.e., young onset). Based on a recent retrospective analysis conducted in Ontario, approximately 0.8% of patients

experienced an onset of parkinsonism symptoms prior to 40 years of age, with an increasing prevalence occurring over the study duration.[31]

  - CADTH considered the inclusion of patients 40 years of age or younger as part of its base-case analyses.

- **Treatment titration not considered:** The sponsor included the maintenance dose only for those patients receiving APO SC or APO SL; however, in its pharmacoeconomic report, the sponsor stated that samples would be distributed at no charge. Although the inclusion of treatment titration costs likely biases results against APO SL, the impact on results is expected to be minimal.

CADTH retained the maintenance dose costs as part of its base case.

- **Target population and market share estimates uncertain:** The sponsor included multiple assumptions to derive the target population, including the proportion of patients treated and optimized on levodopa therapy and the proportion of patients experiencing OFF episodes. Given the lack of available data, the sponsor utilized clinical expert opinion to inform these model parameters; however, regional differences in practice and patient demographics may influence these estimates and subsequently lead to the under- or overestimation of the target population, which substantially impacts the resulting budget impact. The clinical expert consulted by CADTH indicated that 100% of patients would be administered levodopa/carbidopa, with only a small subset of patients not receiving treatment. Further, although the sponsor assumption that [redacted]% of patients would experience OFF episodes, this value is associated with substantial uncertainty, as the occurrence of these episodes would vary by subgroup (e.g., duration of levodopa exposure, time since diagnosis) and the majority of patients will eventually experience at least 1 OFF episode.

The clinical expert consulted by CADTH also highlighted that both patients and physicians are reluctant to use APO SC, given the administration challenges. The clinical expert further indicated that the introduction of APO SL presents a more convenient treatment alternative and may potentially capture the entire market share for apomorphine treatments and increase the number of patients willing to try apomorphine treatment.

As part of its base-case reanalyses, CADTH adjusted the proportion of patients taking levodopa/carbidopa to 100% and explored a 10% increase in the proportion of patients experiencing OFF episodes. A scenario where APO SL captures all of the market share for apomorphine was conducted by CADTH. Similarly, a scenario where a 100% growth in market size due to the introduction of APO SL was explored.

An issue for consideration is the potential price reduction for APO SC, as outlined previously, where a respective price reduction of 45% and 60% would be required for APO SL to have similar total costs. CADTH explored the price reduction as part of its scenario analyses.

CADTH Reanalyses of the Budget Impact Analysis

Based on the limitations identified by CADTH, patients 40 years of age or younger were included in the reanalyses, and it was assumed 100% of patients would receive levodopa/carbidopa as part of CADTH's base-case analyses (Table 23).

Table 23: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Inclusion of early onset parkinsonism patients	Excluded	0.8% of parkinsonism population
2. Proportion receiving levodopa/carbidopa	[redacted]%	100%
CADTH base case	–	Reanalyses 1 and 2

The results of the CADTH stepwise reanalyses are presented in summary format in Table 24 and a more detailed breakdown is presented in

Table 25. Based on the CADTH base case, the expected budget impact for adult patients with PD receiving acute, intermittent treatment of OFF episodes is expected to be $1,618,459 in year 1, $4,010,565 in year 2, and $6,200,845 in year 3, with a 3-year budget impact of $11,829,869.

Scenario analyses were conducted using the CADTH base case, with the increased market growth having the largest impact on results ($26,921,917 over 3 years). When applying a 45% or 60% price reduction to APO SL (i.e., a price where APO SL represented a cost saving compared with the price reductions suggested for APO SC [50% or 65%] at respective WTP thresholds of $100,000 and $50,000 per QALY), the overall 3-year cost expenditures were $7,089,211 and $5,492,178, respectively.

Table 24: Summary of the CADTH Reanalyses of the Budget Impact Assessment

Stepped analysis	Three-year total
Submitted base case	$[redacted]
CADTH reanalysis 1: Inclusion of early onset parkinsonism patients	$10,646,882
CADTH reanalysis 2: Proportion patients receiving levodopa/carbidopa	11,642,838
CADTH base case	**$11,829,869**

Table 25: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	[redacted]	[redacted]	[redacted]	[redacted]
	New drug	[redacted]	[redacted]	[redacted]	[redacted]
	Budget impact	[redacted]	[redacted]	[redacted]	[redacted]
CADTH base case	Reference	4,687,403	11,615,450	17,958,969	34,261,822
	New drug	6,305,862	15,626,015	24,159,814	46,091,690
	Budget impact	**1,618,459**	**4,010,565**	**6,200,845**	**11,829,869**
CADTH scenario analysis 1: 45% price reduction for APO SL and 50% reduction APO SL	Reference	2,109,331	5,226,953	8,081,536	15,417,820
	New drug	3,079,215	7,630,338	11,797,477	22,507,030
	Budget impact	**969,884**	**2,403,386**	**3,715,941**	**7,089,211**
	Reference	1,476,532	3,658,867	5,657,075	10,792,474

Stepped analysis	Scenario	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
CADTH scenario analysis 2: 60% price reduction APO SL and 65% reduction APO SL	New drug	2,227,924	5,520,826	8,535,902	16,284,652
	Budget impact	**751,392**	**1,861,959**	**2,878,827**	**5,492,178**
CADTH scenario analysis 3: 50% of patients experience OFF episodes	Reference	5,150,992	12,764,231	19,735,131	37,650,353
	New drug	6,929,518	17,171,445	26,549,246	50,650,209
	Budget impact	**1,778,526**	**4,407,214**	**6,814,115**	**12,999,856**
CADTH scenario analysis 4: APO SL 100% market share	Reference	4,687,403	11,615,450	17,958,969	34,261,822
	New drug	6,194,286	15,349,529	23,732,331	45,276,145
	Budget impact	**1,506,883**	**3,734,078**	**5,773,362**	**11,014,324**
CADTH scenario analysis 5: APO SL increases market growth 100%	Reference	4,687,403	11,615,450	17,958,969	34,261,822
	New drug	8,370,624	20,742,525	32,070,591	61,183,739
	Budget impact	**3,683,221**	**9,127,074**	**14,111,622**	**26,921,917**

APO = apomorphine hydrochloride; SL = sublingual.

Source: Sponsor's pharmacoeconomic submission.[2]

References

1. CDR submission: kynmobi (apomorphine hydrochloride), soluble film: 10 mg, 15 mg, 20 mg, 25 mg and 30 mg, sublingual [CONFIDENTIAL sponsor's submission]. Mississauga (ON): Sunovion Pharmaceuticals Canada Inc.; 2020 Jun 25.
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3. Clinical Study Report: CTH-300. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy, safety and tolerability of APL-130277 in levodopa responsive patients with Parkinson's disease complicated by motor fluctuations ("OFF" episodes) [CONFIDENTIAL internal sponsor's report]. Marlborough (MA): Sunovion Pharmaceuticals Inc.; 2018 Mar 7.
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