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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Apomorphine (Movapo)

(Paladin Labs Inc.)

Indication: 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

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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
CDR	CADTH Common Drug Review
H&Y	Hoehn and Yahr
ICUR	incremental cost-utility ratio
PD	Parkinson's disease
QALY	quality-adjusted life-year
SoC	standard of care
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Apomorphine hydrochloride pen, 10 mg/mL (Movapo)
Study Question	"What is the cost-effectiveness of apomorphine injections supplied as pre-filled pens (10 mg/mL) given as adjunct therapy in the treatment of acute, intermittent hypomobility "off" episodes in patients with advanced PD [Parkinson's disease] compared to SoC [standard of care] oral PD medications?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with advanced PD who experience acute, intermittent hypomobility, referred to as "off" episodes
Treatment	Apomorphine pen, dosed as needed, as adjunct to SoC PD medications (e.g., levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors)
Outcome	QALYs
Comparator(s)	SoC (oral PD medications alone)
Perspective	Canadian publicly funded health-care payer
Time Horizon	5 years
Results for Base Case	ICUR = $72,705 per QALY
Key Limitations	CDR identified the following key limitations: • Reduction in time spent in "off" state overestimated: The model derived its only efficacy parameter from an SR with heterogeneous studies and patient populations, which used oversimplified meta-analytic methods, resulting in an effect substantially larger than that seen in the available RCT. • Change in effect over time not considered: the model did not allow for disease progression or the attenuation of response over time, or for discontinuation of treatment due to lack or loss of efficacy or intolerable AEs. • Model structure does not accurately reflect the heterogeneity of the condition: All patients in the model were assumed to have a disease severity of H&Y stage of 3.6, which does not consider the relationship between H&Y stage and "off" time, and the impact on treatment efficacy, dosing, disease progression, mortality, AEs, health care resource use, or utilities based on severity of disease. • Dose of apomorphine is underestimated: The manufacturer's base case is based on the average dose from the previously mentioned SR, which is not aligned to reflect wastage based on the dosing requirements in the product monograph.
CDR Estimate	CDR addressed these limitations where possible by using the mean reduction in time spent in the "off" state from the available RCT, incorporating disease progression as per previously published PD models, and incorporating wastage as outlined in the product monograph. CDR's base-case reanalysis estimated the cost-effectiveness of apomorphine + SoC compared with SoC to be $242,004. 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.

AE = adverse event; CDR = CADTH Common Drug Review; COMT = catechol-O-methyltransferase; H&Y = Hoehn and Yahr; ICUR = incremental cost-utility ratio; MAO-B = monoamine oxidase B; PD = Parkinson's disease; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SoC = standard of care; SR = systematic review.

Drug	Apomorphine hydrochloride (Movapo)
Indication	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.
Reimbursement Request	As per indication
Dosage Form	Pre-filled pens, 10 mg/mL, 3 mL
NOC Date	November 22, 2016
Manufacturer	Paladin Labs, Inc.

Executive Summary

Background

Apomorphine (Movapo) is a dopamine agonist indicated in Canada 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).[1] It is available in 3 mL (30 mg) pre-filled disposable multi-dose pens for subcutaneous injection at a submitted price of $42.95 per pen or $1.43 per mg.[2] The recommended starting dose of apomorphine is 0.2 mL (2 mg) as needed to treat recurring “off” episodes, to be titrated by 0.1 mL (1 mg) 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. A non-5HT3 antagonist concomitant antiemetic should be started at least two days prior to the initial dose of apomorphine and continued based on dosing recommendations for the antiemetic, and reassessed periodically.[1]

The manufacturer submitted a cost-utility analysis comparing apomorphine (with concomitant domperidone) as an adjunct to standard of care (SoC) oral therapy versus SoC alone for the treatment of “off” episodes in patients with advanced PD.[2] 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 toward a less severe “off” state after the first one-year cycle based on the findings of a published systematic review,[3] 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 (H&Y) stage of 3.6 based on the same systematic review;[3] H&Y stage was not otherwise considered in the model. As SoC was assumed to be the same between groups, only adverse events (AEs) associated with apomorphine were included, with utility decrements and resource costs applied for two months in the first year of treatment.

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). Apomorphine was associated with a higher cost driven by the drug cost of apomorphine and more QALYs due to patients in the apomorphine group transitioning to less severe “off” states with higher utilities and remaining there for the remainder of the time horizon. No difference in total life-years was reported between treatments. At a willingness to pay (WTP) threshold of $50,000 per QALY,

the probability of apomorphine plus SoC being cost-effective compared with SoC alone was reported to be 27%, while at a WTP of $100,000, the probability of being cost-effective increased to 67%.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the model submitted by the manufacturer.

Firstly, the model structure did not consider H&Y stages independently or the relationship between discrete H&Y 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 a systematic review with heterogeneous studies and patient populations and oversimplified meta-analysis methods as the source of the model's only efficacy input is highly uncertain. Moreover, the model did not allow for disease progression or the attenuation of response over time, or for discontinuation of treatment due to lack or loss of efficacy or intolerable AEs. Additionally, the long-term efficacy of apomorphine is associated with uncertainty. Finally, the manufacturer's base case assumed the average dose from the previously mentioned systematic review, which is inconsistent with the Health Canada–recommended storage and stability instructions in the product monograph.[1]

CDR attempted to address these issues. The CDR base-case analysis included "off" state transitions derived from those used in previous models[4,5] to incorporate progression, efficacy (mean reduction in time spent in the "off" state) as measured in the longest randomized controlled trial,[6,7] and medication costs consistent with the product monograph's pen disposal recommendations. In this analysis, the incremental cost-utility ratio (ICUR) of apomorphine plus SoC compared with SoC alone was $242,004 per QALY.

Conclusions

CDR undertook a base case reanalysis based on 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 per day. CDR was unable to test the impact of a model structure that considered distinct H&Y stages and discontinuation of treatment, which leads to uncertainty in the CDR base case ICUR.

Reanalyses by CDR concluded that, at the submitted price, the base case 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 WTP threshold below $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.

Information on the Pharmacoeconomic Submission

Summary of Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a Markov state-transition model comparing apomorphine (used concomitantly with domperidone) as an adjunct to the standard of care (SoC; oral therapy for Parkinson's disease [PD]) versus SoC alone for the treatment of "off" episodes in patients with advanced PD.[2] The base case was a probabilistic analysis of 5,000 simulations using a five-year time horizon with yearly cycles conducted from the perspective of a Canadian health care payer. Costs and benefits were discounted after one year at a rate of 1.5%. A half-cycle correction was incorporated.

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 (see Figure 1).

The initial distribution of patients within the health states was derived from the mean baseline hours spent in the "off" state of 5.86 (standard deviation, 0.5) hours per day reported in a double-blind 28-day randomized controlled trial (APO 202; Dewey et al. [2001])[6,7] and an assumption that patients are awake for 16 hours per day. The apomorphine group transitioned toward a less severe "off" state after the first one-year cycle, with the proportions in each state based on the reduction in time spent in the "off" state reported in a published systematic review (Deleu et al. [2004][3]), while those in the SoC group remained in their original "off" state. With the exception of mortality, which was based on Statistics Canada 2010-2012 life tables and adjusted based on the relative risk of death for patients with PD reported in Liou et al. (2009),[8] no further transitions were allowed after the first cycle. Patients neither improved nor progressed in terms of disease severity or time spent in the "off" state for the remainder of the model, nor did any patients discontinue treatment.

All patients in the manufacturer's model were assumed to have a disease severity score (measured by Hoehn & Yahr [H&Y] stage) of 3.6 based on Deleu et al. (2004).[3] As previous models and the studies used by the manufacturer as data sources[4,5,8-10] reported results by each H&Y stage, the manufacturer interpolated inputs from H&Y stages 3 and 4 from these sources to estimate values for H&Y 3.6.

Utility estimates for each of the "off" stages were interpolated from those used in Lowin et al. (2011).[5]

Health care utilization was assumed to vary between "off" stages based on the results of a UK observational study, Findley et al. (2011),[9] and again an estimate for patients at H&Y stage 3.6 was interpolated from stage-specific data (see Table 11). Costs for health care use were from the Ontario Case Costing Initiative in 2010-2011,[11] and physician visit and diagnostic scan costs were taken from the Ontario Schedule of Benefits for Physician Services.[12]

As SoC was assumed the same in both treatment groups, only adverse events (AEs) associated with apomorphine were included in the manufacturer's model. AE incidence was as reported in the product monograph,[1] based on those observed in Dewey et al. (2001).[6,7] Utility decrements were applied for two months in the first year of apomorphine treatment for

select AEs using values reported by Walter and Odin (2015).[4] Health care resource costs for all AEs were also assumed to occur over the two-month duration (Table 12).

Manufacturer's Base Case

The manufacturer's base case results reported an incremental cost-utility of $72,705 per quality-adjusted life-year (QALY) (Table 2).The difference in costs was driven by the higher cost of apomorphine and domperidone compared with SoC, while the difference in QALYs was driven by patients in the apomorphine group transitioning to better "off" states with higher utilities and remaining there for the remainder of the time horizon (Table 15). The manufacturer noted that no difference in total life-years was found between treatment groups. At a willingness to pay (WTP) threshold of $50,000 per QALY, the probability of apomorphine plus SoC being cost-effective compared with SoC alone is 27%, while at a WTP of $100,000, the probability of being cost-effective is 67% (Table 2).

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Apomorphine ($)	Total QALYs	Incremental QALYs of Apomorphine	Incremental Cost Per QALY ($)
Standard of Care	66,269		1.86		
Apomorphine + Standard of Care	83,868	17,599	2.10	0.24	72,705

QALY = quality-adjusted life-year.

Note: Costs and QALYs discounted at 1.5% after the first year.

Source: Manufacturer's pharmacoeconomic submission.[2]

The manufacturer also conducted a deterministic analysis, resulting in an incremental cost per QALY of $72,300.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted probabilistic scenario analyses varying the time horizon, discount rate, relative effectiveness of apomorphine in terms of percentage reduction in time spent in an "off" state, and apomorphine dose. The model was most sensitive to changes in the efficacy of apomorphine and the dosage used per day. Varying the reduction in time spent in an "off" state from 58% to 33% led to an incremental cost-utility ratio (ICUR) range of $52,302 to $128,718 per QALY, while varying the apomorphine dose per day from 9 mg to 15 mg led to an ICUR range of $38,779 to $97,470 per QALY.

Limitations of Manufacturer's Submission

Model structure does not accurately reflect the heterogeneity of the condition: In the submitted model, all patients were assumed to have a disease severity of H&Y stage 3.6; thus, data were interpolated from multiple sources, rather than considered as discrete H&Y stage–based health states as has been done in previous PD models. Given that the stages of disease are considered as discrete categories in practice, using a single interpolated disease severity score is not appropriate because it does not consider the relationship between H&Y stage and "off" time and the impact on treatment efficacy, dosing, progression, mortality, AEs, health care resource utilization, or utilities based on severity of disease, or allow these considerations to be explored. Additionally, the use of a one-year cycle length is not sufficiently granular to reflect how PD is treated in Canadian practice,

based on feedback from the clinical expert consulted by the CADTH Common Drug Review (CDR), and differs from previous advanced PD models.[4,5,10]

Reduction in time spent in "off" state is overestimated: For efficacy, the manufacturer's model used the "synopsis" result for reduction in time spent in the "off" state from a 2004 descriptive systematic review[3] of intermittent apomorphine use. The methods used to derive this result are unclear and do not appear to be from a formal meta-analyses, nor do attempts to control for heterogeneity between study types or patient populations appear to have been made. CDR considered it more appropriate to use a 29% mean time spent in the "off" state reduction calculated from the 28-day APO 202 trial (Dewey et al. [2001], Table 18)[6,7].

Disease progression is not considered in the model: PD is a chronic and progressive disease where patient health and quality of life worsen over time.[13] Additionally, treatments for PD tend to lose efficacy as the disease progresses.[13] The manufacturer's model does not account for either of these factors. After the first cycle, where patients receiving apomorphine may transition into a better "off" state, no further transitions take place with the exception of mortality; patients remain in their assigned "off" states for the entire time horizon or until they die. The assumptions that treatment efficacy and quality of life remain constant over the duration of the model are unlikely to be appropriate based on feedback from the clinical expert consulted by CADTH and previously published economic evaluations for advanced PD. CDR reviewers incorporated transition probabilities between "off" states derived from a previous model[4] to more accurately reflect disease progression (Table 18).

Discontinuation not incorporated: The manufacturer's model does not allow for patients to discontinue treatment with apomorphine due to lack or loss of efficacy or to intolerable side effects or AEs. This is unlikely to reflect clinical practice, based on feedback from the clinical expert, patient input, and discontinuation rates from the clinical trials.

Dosing of apomorphine is underestimated: The manufacturer's base case used the average dose reported in Deleu et al. (2004)[3] of 12.5 mg per day of apomorphine. The manufacturer did not consider the potential wastage, given that the product monograph[1] states that opened apomorphine pens should be discarded after 48 hours. When used as recommended (and assuming patients do not require 20 mg per day for multiple days), patients will use or discard 15 mg per day of apomorphine (a 30 mg vial every 2 days). If more than one vial every two days is required, the incremental cost of apomorphine will be greater than estimated.

CADTH Common Drug Review Reanalyses

As described above, CDR reviewers considered the 29% mean reduction in time spent in the "off" state calculated from Dewey et al. (2001)[6,7] to be a more reliable measure of efficacy than the 46% reported in Deleu et al. (2004)[3]. Additionally, CDR considered the inclusion of disease progression in terms of increasing time spent in "off" periods over time as described in Walter and Odin (2015),[4] and apomorphine dosing consistent with the product stability described in the product monograph (15 mg per day) to be more appropriate.

Table 3: Summary of Results of CDR's Base Case

	Total Costs ($)	Incremental Cost of Apomorphine ($)	Total QALYs	Incremental QALYs of Apomorphine	Incremental Cost Per QALY ($)
Standard of Care	72,619	29,260	1.77	0.12	242,004
Apomorphine + Standard of Care	101,878		1.89		

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

Note: Costs and QALYs discounted at 1.5% after the first year.

Source: Manufacturer's pharmacoeconomic submission.[2]

CDR conducted a price-reduction analysis using the manufacturer's and CDR's base case analyses (Table 4). Based on the CDR base-case analysis, a price reduction of 48% resulted in apomorphine being cost-effective at a WTP of $100,000 per QALY, while a reduction of 65% would be required for apomorphine to be cost-effective at a WTP of $50,000 per QALY.

Table 4: CDR Reanalysis Price-Reduction Scenarios

Price	Price Per mg ($)	ICUR of Apomorphine + SoC Versus SoC	
		Manufacturer's Base Case ($/QALY)	CDR Base Case ($/QALY)
Submitted	1.43	72,705	242,004
10% reduction	1.29	61,219	215,507
19% reduction	1.16	**48,887**	187,896
20% reduction	1.15	48,355	185,185
30% reduction	1.00	36,586	155,409
40% reduction	0.86	23,199	124,014
48% reduction	0.74	**13,902**	**98,878**
50% reduction	0.72	11,277	93,575
59% reduction	0.59	**Dominant**	65,775
60% reduction	0.57	Dominant	62,912
65% reduction	0.46	Dominant	**47,715**
70% reduction	0.43	Dominant	32,905

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Issues for Consideration

Other dosage forms: The manufacturer submitted apomorphine 3 mL pre-filled multi-dose pens for consideration by CDR; however, based on the product monograph, apomorphine 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 2 mL ampoules of apomorphine may differ from that of 3 mL pre-filled pens.

Usability of injections: Pre-filled multi-dose pens for injection are easier to use than ampoules or pre-filled syringes; however, the pens may still be difficult to use for patients already in the midst of an "off" period, necessitating the assistance of a caregiver to inject the medication, which may not be an option for all patients.

Subsequent treatments: The use of intermittent apomorphine may potentially delay the need for more intrusive therapies such as deep brain stimulation or levodopa/carbidopa intestinal gel in some patients. However, as the manufacturer's model does not incorporate these therapies into the downstream effects of apomorphine use, it is not possible to estimate any benefit, harm, quality of life, or cost differences that may occur. This increases uncertainty in the estimated cost-effectiveness of apomorphine.

Patient Input

Input was received from Parkinson Canada and the Parkinson Society of British Columbia. Feedback from the patient groups indicated that new, longer lasting medications that limit or eliminate "off" times are needed. Issues such as unpredictable "off" times were reported to negatively impact patients' quality of life, as did the progressive nature of the disease and increasing amount of time spent in an "off" state. Most patients who had apomorphine experience reported an improvement in treatment "wearing off" effects, reducing "off" times and thereby improving quality of life, though this response was not uniform for all apomorphine users. Some patients who had received deep brain stimulation treatment also reported carrying apomorphine injections in the event of sudden PD symptoms such as dystonia. Apomorphine pens were considered relatively easy to administer, although more difficult than other PD medications. Additionally, if "off" time symptoms had already started, injection might not be possible without the help of others, which was considered a challenge. The manufacturer's submission did not consider the progressive nature of PD or the impact of this in the time spent in an "off" state, nor did it consider discontinuation due to lack of efficacy or increasing dose over time. See Appendix 1 in the CDR Clinical Report for the full Patient Input Summary.

Conclusions

CDR undertook a base case reanalysis based on 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 per day. CDR was unable to test the impact of a model structure that considered distinct H&Y stages, discontinuation of treatment, and the possible delay of subsequent treatments, which leads to uncertainty in the CDR base case ICUR.

Reanalyses by CDR concluded that, at the submitted price, the base case 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 WTP threshold below $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.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in Table 5, and as such the table may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table for Parkinson's Disease

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Apomorphine (Movapo)[a]	10 mg/mL	3 mL pen	$42.9520[b] per pen	0.2 to 0.6 mL per "off" episode, maximum 2 mL daily	4.30 to 21.48	7,839 to 10,452
Current Therapies Used in Moderate to Advanced Parkinson's Disease						
Oral Levodopa/Decarboxylase Inhibitor Combinations						
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	0.44 to 1.48	162 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	0.77 to 5.69	282 to 2,078
Levodopa/ benserazide (Prolopa)	50 mg/12.5 mg 100 mg/25 mg 200 mg/50 mg	Capsule	0.2998 0.4936 0.8286	400 mg to 800 mg of levodopa daily in 4 to 6 doses	1.97 to 3.31	721 to 1,210
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 150 mg/37.5 mg/200 mg	Tablet	1.7371	600 mg to 1,600 mg of entacapone daily in multiple doses	5.21 to 13.90	1,902 to 5,072
Non-Ergolinic Dopamine Agonists						
Rotigotine (Neupro)	2 mg/24 h 4 mg/24 h 6 mg/24 h 8 mg/24 h	Patch	3.5400[c] 6.5000[c] 7.2702[c] 7.2704[c]	2 mg to16 mg daily	3.54 to 14.54	1,292 to 5,307
Pramipexole (generics)	0.25 mg 0.50 mg 1 mg 1.5 mg	Tablet	0.2628 0.5257[d] 0.5257 0.5257	1.5 mg to 4.5 mg in 3 equal doses	0.79[e] to 2.37	288 to 864
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	0.85 to 3.75	310 to 1,369
Ergolinic Dopamine Agonists						
Bromocriptine (Generics)	2.5 mg 5 ng	Tablet Capsule	0.9978 1.4937	2.5 to 40 mg daily, in 2 to 3 doses	1.00 to 11.95	364 to 4,362

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
MAO-B Inhibitors						
Rasagiline (Azilect)	0.5 mg 1 mg	Tablet Tablet	3.6050[c]	0.5 to 1 mg daily	3.60	1,315
Selegiline (generics)	5 mg	Tablet	0.5021	5 mg twice daily	1.00	367
Other						
Amantadine (generics)	100 mg	Capsule	0.5252	100 mg once or twice daily	0.53 to 1.05	192 to 383

CDR = CADTH Common Drug Review; COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; ODB = Ontario Drug Benefit; PD = Parkinson's disease.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed August 2017) [14] unless otherwise indicated and do not include dispensing fees.

The clinical expert consulted by CDR noted that in the absence of apomorphine or other medication available specifically for reducing "off" periods, patients experiencing substantial "off" periods may have their levodopa/carbidopa divided into more frequent doses and/or increase their dose of adjunctive therapies. Patients with more advanced PD are considered for deep brain stimulation or levodopa/carbidopa intestinal gel.

[a] Manufacturer's product monograph indicates that subcutaneous apomorphine is also supplied as ampoules; however this form was not included as part of submission.

[b] Manufacturer's submitted price;[2] assumes excess medication disposed of after 48 hours.[2] Assumes at least one dose required every 48 hours.

[c] National wholesale price as reported in Quintiles IMS Delta PA database (August 2017).

[d] Saskatchewan formulary (August 2017).[15]

[e] The 0.5 mg tablet is not a benefit of the ODB formulary. However, the 1 mg tablet is scored.

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Apomorphine Plus SoC Relative to SoC Alone (CDR Reanalysis)?

Apomorphine Hydrochloride + SoC Vs. SoC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (Total)					X	
Drug Treatment Costs Alone					X	
Clinical Outcomes	X					
Quality of Life		X				
Incremental CE Ratio or Net Benefit Calculation	$269,810 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SoC = standard of care.

Appendix 3: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

Table 8: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

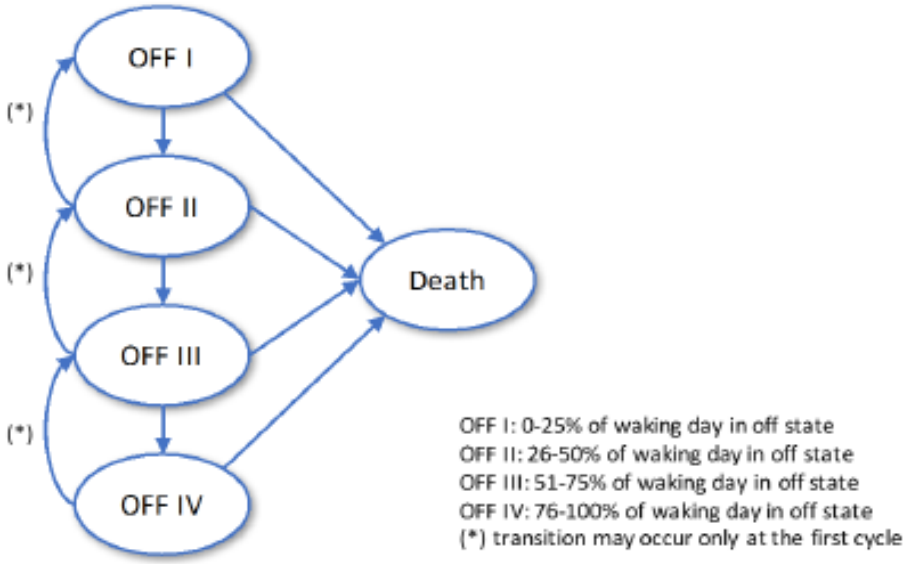
Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a Markov state-transition model comparing apomorphine (with concomitant domperidone) as an adjunct to standard of care (SoC) oral therapy versus SoC alone for the treatment of "off" episodes in patients with advanced Parkinson's disease (PD).[2] The base case was a probabilistic analysis of 5,000 simulations with a five-year time horizon with yearly cycles, conducted from the perspective of a Canadian health care payer, 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 (see Figure 1); patients entered the model in one of the four health states.

Figure 1: Model Structure Overview



Source: Manufacturer's pharmacoeconomic submission, Figure 2.[2]

The initial distribution of patients within the health states was based on a gamma distribution derived from the mean baseline hours spent in the "off" state of 5.86 (standard deviation, 0.5) hours per day reported in Dewey et al. (2001)[6,7] and an assumption that patients are awake for 16 hours daily. The apomorphine group transitioned toward a less severe "off" state after the first one-year cycle, based on the summary findings for reduction in time spent in the "off" state reported in a published systematic review, Deleu et al. (2004),[3] while those in the SoC group remained in their original "off" state (see Table 9).

While the structure in Figure 1 shows possible transitions to improve (less severe) "off" states, these were not in fact incorporated into the model. With the exception of mortality, which was based on Statistics Canada 2010-2012 life tables and adjusted based on the relative risk of death for patients with PD reported in Liou et al. (2009),[8] no further transitions were allowed after the first cycle. Patients neither improved nor progressed in terms of disease severity or time spent in "off" states for the remainder of the model.

Table 9: Distribution of Patients Across Model Health States

Health State	Apomorphine + SoC		SoC	
	Initial Distribution	After First Cycle	Initial Distribution	After First Cycle
"Off" I (0% to 25% waking time in "off" state)	22.0%	76.8%	22.0%	22.0%
"Off" II (26% to 50% waking time in "off" state)	60.2%	23.2%	60.2%	60.2%
"Off" III (51% to 75% waking time in "off" state)	17.4%	0.0%	17.4%	17.4%
"Off" IV (76% to 100% waking time in "off" state)	0.4%	0.01%	0.4%	0.4%

SoC = standard of care.

Source: Manufacturer's pharmacoeconomic submission, Table 12.[2]

All patients in the manufacturer's model were assumed to have a Hoehn and Yahr (H&Y) score of 3.6, based again on the synopsis findings of Deleu et al. (2004).[3] As previous models and the studies used as data sources[4,5,8-10] have reported results by varying H&Y stage, the manufacturer interpolated inputs from H&Y stages 3 and 4 to estimate values for H&Y 3.6.

Utility estimates for each of the "off" stages were interpolated from those used in Lowin et al. (2011)[5] (see Table 10).

Table 10: Health Utilities for "Off" State Categories

Resource	Utilities Reported in Lowin et al. (2011)[5]		Interpolated for Model Value H&Y 3.6
	H&Y 3	H&Y 4	Initial Distribution
"Off" I (0% to 25% waking time in "off" state)	0.643	0.387	0.489
"Off" II (26% to 50% waking time in "off" state)	0.555	0.299	0.401
"Off" III (51% to 75% waking time in "off" state)	0.467	0.211	0.313
"Off" IV (76% to 100% waking time in "off" state)	0.379	0.123	0.225

H&Y= Hoehn and Yahr.

Source: Adapted from manufacturer's pharmacoeconomic submission, Table 16[2]

Health care utilization was assumed to vary between "off" stages based on the results of a UK observational study, Findley et al. (2011),[9] and again an estimate for patients at H&Y stage 3.6 was interpolated from stage-specific data (see Table 11). Costs for health care use were from the Ontario Case Costing Initiative in 2010-2011,[11] and physician visit and diagnostic scan costs were taken from the Ontario Schedule of Benefits for Physician Services.[12]

Table 11: Health Care Resource Use and Unit Costs Used in the Model by "Off" State

Annual Resource Utilization (Derived From Findley et al.[9])	Health State				Unit Cost ($)	Source for Unit Cost
	"Off" I	"Off" II	"Off" III	"Off" IV		
Hospitalization	0.52	0.72	1.20	1.20	17,892.71	OCCI CMG Grouper: 023, 2010-2011
Specialist Visits	2.90	2.81	2.80	2.80	158.11	Ontario SoB, average of A185, A180, A186, A183, A184, C185, C180, C186
GP Visits	3.18	3.95	3.90	3.90	61.55	Ontario SoB, average of A005, A006
MRI	0.25	0.43	0.60	0.60	46.38	Ontario SoB, average X421, E875
CT	0.34	0.48	0.50	0.50	61.35	Ontario SoB, average X400, X401, X188

CT = computed tomography; GP = general practitioner; MRI = magnetic resonance imaging; OCCI = Ontario Case Costing Initiative; SoB = Schedule of Benefits.

Source: Adapted from manufacturer's pharmacoeconomic submission, Table 20.[2]

As SoC was used in both treatment groups, only adverse events (AEs) associated with apomorphine use were included in the manufacturer's model. AE incidence was as reported in the product monograph,[1] based on those observed in Dewey et al. (2001),[6,7] a month-long randomized controlled trial. Utility decrements were applied for two months in the first year of treatment for dyskinesia, dizziness or postural hypotension, and chest pain/pressure/angina, and were derived from Walter and Odin (2015).[4] Health care resource costs for all AEs were also assumed to occur over two months in the first year (Table 12).

Table 12: Adverse Event Prevalence and Health Care Cost

Adverse Event	Incidence	Resource Use	Disutility Applied for 2 Months	Cost ($)
Yawning	40%	One GP visit, but apparently not an additional visit (cost = $0)	0	0.00
Dyskinesias	35%	One specialist consultation	33%	158.11
Drowsiness or somnolence	35%	One GP visit	0	61.55
Nausea	35%	One GP visit; domperidone 10 mg for 2 months	0	168.47
Dizziness or postural hypotension	25%	Two specialist consultations	0.160	316.23
Rhinorrhea	20%	One GP visit	0	61.55
Chest pain / pressure / angina	15%	One GP visit	0.180	61.55
Hallucination or confusion	10%	One specialist visit; quetiapine 300 mg daily for 2 months	0	199.83
Edema / swelling of extremities	10%	One GP visit	0	61.55
Injection site reactions	27%	One specialist consultation	0	158.11

GP = general practitioner.

Source: Adapted from manufacturer's pharmacoeconomic submission, Tables 17 and 21.[2]

The manufacturer also conducted a deterministic analysis, as well as scenario analyses considering a 10-year time horizon, discount rates of 0 and 3%, the highest and lowest percentage "off" time reductions from studies included in Deleu et al. (2004),[3] and the average dose of apomorphine from the clinical trials or considering pen wastage as recommended in the product monograph.

Table 13: Model Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Reduction in "off" time for apomorphine + SoC compared with SoC alone derived from Deleu et al. (2004),[3] a systematic review. Beta distribution was used to test uncertainty.	Methods used by Deleu 2004 to derive their synopsis results are unclear and do not appear to be formal meta-analyses, nor do attempts to control for heterogeneity between study types or patient populations appear to have been made. Additionally, as included studies range from 1989 to 2001, and both clinical practice and available SoC treatments have changed, the relative effectiveness of apomorphine + SoC versus SoC currently is uncertain. See CDR Clinical Report, Appendix 7, for an appraisal of the Deleu systematic review.
Natural History	Natural history (progression) was not modelled. Initial "off" state patient distribution and continuing SoC group proportions derived from Dewey et al. (2001) (APO 202 CSR).[7] Percentage of males was calculated from Stats Canada prevalence and 2017 projections of the Canadian population. Patients were assumed to be awake for an average of 16 hours per day.	Other models in PD assume the disease continues to progress over time.[4,5,10] The clinical expert consulted by CDR did not consider the assumption of no progression to be valid. Acceptable Acceptable
Utilities	Derived from Lowin et al. (2011),[5] calculated using the mean H&Y stage from Deleu et al. (2004)[3] Disutilities due to AEs derived from Walter and Odin 2015[4]	Lowin et al. is a frequently used source of utilities. Using only a mean H&Y stage rather than incorporating it into model health states appears unique. Walter and Odin adjusted utilities in H&Y stages 4 and 5 with decrements from H&Y 3 rather than use the minimal data from Lowin et al. in these stages alone.
Adverse Events	Incidence rates taken from apomorphine monograph,[1] which are based on those observed in Dewey et al. (2001).[6,7] SDs of 10% assumed, applied in first cycle only. Disutilities (dyskinesias, postural hypotension/dizziness, chest pain/pressure/angina) applied for two months	Clinical expert consulted by CDR believes most AEs would continue beyond 1 year and that some patients would discontinue therapy due to them.
Mortality	Statistics Canada Life Tables multiplied by relative risk of death derived from Liou et al. (2009),[8] calculated from > 65-year-old category and using mean H&Y stage from Deleu et al. (2004)[3]	Uncertain. Use of 65+ age group may be an issue as all patients in model are < 65 for the entirety of the base case. Additionally, Taiwanese patients may not reflect relative life expectancy of patients in Canada. Statistics Canada Life Tables already include PD patients, but given the 1% to 2% prevalence in the age 65+ population, double counting is unlikely to have impact. Use of mean H&Y stage is unique. No other publications assessing PD-specific mortality were identified.
Resource Use and Costs		
Drug	Apomorphine cost provided by the manufacturer, domperidone from ODB Formulary SoC assumed same between groups	Acceptable Assumption that SoC is the same for both arms is generally acceptable, though the clinical trials did

Data Input	Description of Data Source	Comment
		note a small increase in the apomorphine group in levodopa (oral PD drug) use. Assumption that SoC cost is $0 for both treatments is not appropriate, but unlikely to affect the overall result.
	Apomorphine dose assumed constant over time Average dose based on Deleu et al. (2004)[3]	Unacceptable. Dose increases are likely over time as disease progresses.
Administration	None	Acceptable. Apomorphine self-administered (or caregiver administered) and initialization likely incorporated in standard specialist appointment
AEs	Resource use derived from Walter and Odin (2015)[4] and assumption, with costs from Ontario SoB Physician Services[12] (dyskinesia, drowsiness, nausea, dizziness/postural hypotension, rhinorrhea, chest pain/pressure/angina, hallucination/confusion, edema/swelling of extremities, injection site reactions)	Sources acceptable
Health State	Frequencies of hospitalizations, specialist visits, GP visits, MRIs, and CT scans derived from Findley 2011,[9] calculated using mean H&Y stage from Deleu 2004,[3] with costs from OCCI for hospitalization[11] and Ontario SoB Physician Services for others[12]	Acceptable, with the exception of using only a mean H&Y stage. Uncertain whether Findley results are reflective of Canadian practice. OCCI hospitalization data were from 2010-2011; more up-to-date costs could have been used.
	"Off" IV assumed equal to "Off" III due to lack of data	Acceptable

AE = adverse event; CDR = CADTH Common Drug Review; CT = computed tomography; GP = general practitioner; H&Y = Hoehn and Yahr; MRI = magnetic resonance imaging; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; PD = Parkinson's disease; SD = standard deviation; SoB = Schedule of Benefits.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Transitions between states only occur in apomorphine group and only in the first cycle	• Data from other advanced PD treatments indicates that the assumption of no attenuation of response over time is unlikely to be appropriate.[4,5,16,17] • Clinical practice guidelines indicate that the assumption of no disease progression in either group does not reflect the clinical pathway of the disease.[18] • Assumption of no nonresponders or discontinuations may not reflect clinical practice based on feedback from the clinical expert consulted and the patient input received by CDR (see CDR Clinical Report, Appendix 1). • As the benefits, harms, and costs of the possible delaying of subsequent therapies such as DBS and levodopa/carbidopa intestinal gel were not considered in the manufacturer's model, the uncertainty in the cost-effectiveness of apomorphine is increased.
All patients assumed to be at H&Y stage 3.6 based on synopsis mean from Deleu et al. (2004)[3]	• Assumption that response, progression, and dosing are similar between H&Y stages is unlikely to be appropriate and does not account for variation in efficacy and cost. • Assumption that patients do not progress in stage over time is unlikely to be appropriate as PD is a progressive, neurodegenerative condition.[18]

Assumption	Comment
Intermittent apomorphine assumed to cause a 46% reduction in "off" time compared with SoC from Deleu et al. (2004)[3]	• Assumption that the 46% mean reduction in "off" time with apomorphine versus SoC as given when the included studies were conducted (1989 to 2001) is uncertain; given the adjunctive treatments that have become available since, it is possible apomorphine may not have the same relative effect. • Assumption that Deleu's weighted mean (or median where mean was unavailable) synopsis result yields the best available efficacy estimate is unlikely given the lack of proper meta-analysis and lack of assessment of study quality or heterogeneity; included studies were small and varied in design, baseline characteristics, dosage, follow-up duration, and outcomes measured (see Clinical Report, Appendix 7).
Intervention dose assumed to remain constant	• Assumption that dose will remain static over time and that no treatment discontinuation will occur unlikely to reflect clinical practice based on feedback from clinical expert and patient input (see CDR Clinical Report, Appendix 1).
Time horizon and cycle length	• A 5-year time horizon was not considered sufficient by the clinical expert consulted by CDR to reflect the downstream impacts of apomorphine use, given that patients are likely to transition to more advanced therapies (DBS, levodopa/carbidopa intestinal gel) within 5 years. Furthermore, other published economic analyses in PD have used a longer time horizon.[4,5,17] According to the manufacturer's model, only 11% of patients have died by the end of the time horizon. The lack of inclusion of subsequent treatments and their timing and impact increases uncertainty in the cost-effectiveness of apomorphine. A 5-year time horizon was considered in the CDR base case, but as this time horizon is uncertain, additional scenario analyses with longer time horizons were undertaken. If apomorphine is used for longer than 5 years, the ICUR increases. • Other models used in PD have used a 6-month cycle length,[4,5,10,16] which was considered more relevant by the CDR's clinical expert.
50% of apomorphine patients receive maximum recommended dose of domperidone concomitantly	• Assumption that 50% of apomorphine patients receive domperidone may be acceptable, given that the product monograph states 50% of trial patients were able to discontinue antiemetic within 2 months of treatment initiation, although the generalizability to Canadian practice is unknown.
AEs only included for apomorphine group	• Plausible. AEs caused by SoC would happen in both groups given other assumptions. Increased possibility of injuries due to more severe "off" state likely incorporated into hospitalization rate for costs, but not into QoL.
AEs affect cost and quality of life for two months in first year only	• Assumption that AEs have only two months of effect is not appropriate. Feedback from the clinical expert consulted by CDR indicated AEs would likely continue for the duration of treatment, some leading to discontinuation. The manufacturer assumed only select AEs would impact QoL and resource consumption. The clinical expert consulted by CDR indicated other AEs (i.e., drowsiness, nausea, and hallucinations) would also impact QoL, which might be mitigated but not eliminated by additional medications. CDR was able to test the prevalence of the AEs in sensitivity analyses, but was not able to test an extended duration of impact in line with the clinical expert feedback.

AE = adverse event; CDR = CADTH Common Drug Review; DBS = deep brain stimulation; H&Y = Hoehn and Yahr; ICUR = incremental cost-utility ratio; PD = Parkinson's disease; QoL = quality of life; SoC = standard of care.

Manufacturer's Results

The manufacturer's base case results reported an incremental cost-utility of $72,705 per quality-adjusted life-year (QALY) (Table 2).The difference in costs was driven by the higher costs of apomorphine and domperidone ($30,339 and $1,510, respectively, over five years) compared with SoC ($0, relative to apomorphine plus SoC group), offset by the higher health care resource use of the SoC group ($66,605) versus the apomorphine plus SoC group ($52,251). The difference in QALYs was driven by patients in the apomorphine group transitioning to better "off" states with higher utilities and remaining there for the remainder of the time horizon. Although the manufacturer included life-years as an outcome, no difference was found between groups. The manufacturer also conducted a deterministic analysis, resulting in an incremental cost per QALY of $72,300.

Table 15: Results of the Manufacturer's Probabilistic and Deterministic Base Cases

Analysis Type	Treatment	Total Costs ($)	Incremental Cost of Apomorphine ($)	Total QALYs	Incremental QALYs of Apomorphine	Incremental Cost Per QALY ($)
Probabilistic Analysis	Standard of care	66,269	17,599	1.86	0.24	72,705
	Apomorphine + standard of care	83,868		2.10		
Deterministic Analysis	Standard of care	66,605	17,801	1,88	0.25	72,300
	Apomorphine + standard of care	84,406		2.12		

QALY = quality-adjusted life-year.

Note: Costs and QALYs discounted at 1.5% after the first year.

Source: Manufacturer's pharmacoeconomic submission.[2]

While the probabilistic results were presented only in aggregate form, the manufacturer presented their deterministic analysis cost categories separately. While apomorphine, concomitant domperidone, and increased AEs led to extra costs in the apomorphine group, these costs were partially offset by reduced health care resource use due to patients spending more time in less severe "off" states (see Table 16 and Table 17). The manufacturer assumed that as patients who receive apomorphine would not receive a different amount of oral PD medication (SoC) than patients who do not receive apomorphine, the cost of SoC should be $0.

Table 16: Cost Results of Manufacturer's Base Case Deterministic Analysis by Treatment Group

Treatment	Discounted Costs				
	Apomorphine ($)	Other Drugs ($)	Health Care Resources ($)	Adverse Events ($)	Total Cost ($)
SoC	0	0	66,605	0	66,605
Apomorphine + SoC	30,339	1,510[a]	52,251	305	84,406
Incremental Cost (Apomorphine + SoC − SoC)	**30,339**	**1,510[a]**	**−14,354**	**305**	**17,801**

QALY = quality-adjusted life-year; SoC = standard of care.

Note: Costs and QALYs discounted at 1.5% after the first year.

[a] Cost of antiemetic.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 17: QALY Accrual in Manufacturer's Base Case Deterministic Analysis by Treatment Group

Treatment	QALYs Gained Per Health State					
	"Off" I	"Off" II	"Off" III	"Off" IV	AEs	Total QALYs
SoC	0.50	1.12	0.25	0	0	1.88
Apomorphine + SoC	1.61	0.51	0.03	0	−0.02	2.12
Incremental QALYs (Apomorphine + SoC − SoC)	**1.11**	**−0.62**	**−0.23**	**0**	**−0.02**	**0.25**

AE = adverse event; QALY = quality-adjusted life-year; SoC = standard of care.

Costs and QALYs discounted at 1.5% after the first year.

Source: Manufacturer's pharmacoeconomic submission.[2]

At a willingness to pay (WTP) threshold of $50,000 per QALY, the probability of apomorphine plus SoC being cost-effective compared with SoC alone is 27%, while at a WTP of $100,000, the probability of being cost-effective is 67%.

The manufacturer conducted probabilistic scenario analyses varying the time horizon, discount rate, relative effectiveness of apomorphine in terms of percentage reduction in time spent in "off" state, and apomorphine dose. The model was most sensitive to changes in the efficacy of apomorphine as well as the dosage used per day. Varying the reduction in time spent in an "off" state from 58% to 33% led to an incremental cost-utility ratio (ICUR) range of $52,302 to $128,718 per QALY, while varying the apomorphine dose per day from 9 mg to 15 mg led to an ICUR range of $38,779 to $97,470 per QALY.

CADTH Common Drug Review Reanalyses

In order to address the limitations identified in the manufacturer's model, the CADTH Common Drug Review (CDR) conducted a series of reanalyses where possible.

"Off" time reduction: The 46% reduction in "off" time reported in Deleu et al. (2004)[3] for intermittent subcutaneous apomorphine injections is an informal "synopsis" result conducted with unspecified methodology that does not appear to account for the heterogeneity of study designs nor patient populations and as such is highly uncertain. The best available evidence regarding "off" time reduction is therefore from Dewey et al. (2001),[6,7] which reported a change from baseline mean of 1.7 hours when the mean was used (a 29% reduction from the baseline 5.86 hours) and 2.0 hours when the median was used (34% reduction). As a baseline median time spent in "off" was not reported, CDR reviewers considered the 1.7-hour reduction from baseline mean to end point mean to be the most appropriate measure. A 29% reduction in time spent in the "off" state yielded an incremental cost-utility of $161,502 per QALY (Table 18).

Disease progression: Despite the chronic and progressive nature of PD, the manufacturer's model assumed that patients would progress in neither H&Y stage nor in "off" state over the five-year time horizon. CDR reviewers and the CDR clinical expert considered this inappropriate. While the model was not designed to allow for change in H&Y stage over time, it was possible to include transitions between "off" states as was done in Walter and Odin (2015),[4] a model designed to find the cost-effectiveness of continuous subcutaneous apomorphine. Like Walter and Odin, CDR reviewers assumed that the benefit of apomorphine would be a delay in disease progression (in terms of time spent in "off" state) due to improvement in the first cycle, with patients transitioning to worsening "off" states thereafter as time progressed, at the same rates as SoC. Converting the six-month cycle transition probabilities ivaluen value Walter and Odin to year-long cycle transition probabilities using the tool described in Chhatwal et al. (2016)[19] yielded an incremental cost-utility of $94,791 (Table 18).

Apomorphine dose: While Deleu et al. (2004)[3] reported a synopsis dose of 12.5 mg per day of apomorphine, the product monograph specifies that an opened pen should not be used after 48 hours and that excess medication should be discarded. CDR reviewers therefore consider the use (including wastage) of 15 mg per day of apomorphine to be appropriate. The manufacturer's sensitivity analysis using 15 mg per day of apomorphine yielded an ICUR of $97,470 per QALY. If patients require 20 mg per day for multiple days, the incremental cost of treatment will increase, which will increase the estimated ICUR (assuming no impact on clinical benefit).

CDR Base Case: CDR reviewers therefore combined the above factors ("off" time reduction, disease progression, and dose) into the CDR base case, which resulted in an incremental cost of $29,260, an incremental QALY of 0.12, and an ICUR of $242,004 per QALY.

Table 18: CDR Reanalyses Exploring Limitations

Description	Manufacturer's Base Case-Value	CDR value	Incremental Cost ($)	Incremental QALYs	ICUR ($)
Manufacturer's base case	Reference		17,599	0.24	72,705
"Off" time reduction from Dewey et al. (mean)	46%	29%	22,225	0.14	161,502
"Off" time reduction from Dewey et al. (median)	46%	34%	20,775	0.17	122,704
Disease progression; "off" transitions derived from Walter and Odin (2015)[4]	No transitions after first cycle	After first cycle, same in both groups:[a] "Off" I to II: 0.2285 "Off" I to III: 0.0094 "Off" II to III: 0.1393 "Off" II to IV: 0.0032 "Off" III to IV: 0.0842	18,781	0.20	94,791
CDR Base-Case Analysis					
CDR base case	46% "off" reduction No progression 12.5 mg per day	29% "off" reduction Walter and Odin progression 15 mg per day	29,260	0.12	242,004

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Walter and Odin (2015)[4] transition probabilities converted from 6 months to 1 year using the Eigen decomposition tool described in Chhatwal et al. (2016).[19]

At WTP thresholds of $50,000 or $100,000 per QALY, the probability of intermittent apomorphine being cost-effective compared with SoC alone is zero, while the probability at a WTP of $200,000 is 30%.

CDR reviewers also conducted a series of exploratory analyses on the CDR base case to assess the impact of patient entry age, time horizon, "off" state progression halved in the apomorphine group, AE prevalence, removing diagnostic scans but including nursing visits to resource use, waking time, excluding the cost of antiemetics, mortality relative risk, "off" state utilities from Walter and Odin (2015),[4] updating hospitalization costs to 2015-2016 data, and the assumption that patients are at an H&Y stage of 4 rather than 3.6 (see Table 19).

The model was most sensitive to the assumption of slowed progression to more severe "off" states with apomorphine use; halving the rate at which patients using apomorphine transitioned to more severe "off" states compared with those on SoC alone (as was shown in Lowin et al. [2011],[5] when levodopa/carbidopa intestinal gel and deep brain stimulation were compared with SoC) led to an ICUR of $143,196.

The CDR base case uses a five-year time horizon, as it is unlikely that apomorphine will be used for longer than five years. However, should apomorphine be used for longer than five years, the ICUR increases; a 10-year time horizon led to an ICUR of $269,810 per QALY. Additionally, the downstream effects of apomorphine on the timing of subsequent therapies such as deep brain stimulation or levodopa/carbidopa intestinal gel are not possible to explore within the model.

Table 19: CDR Exploratory Reanalyses

Description	CDR Base-Case Value	CDR Reanalysis Value	Incremental Cost ($)	Incremental QALYs	ICUR ($)
CDR base case	Reference		29,260	0.12	242,004
Patient entry age	60 years	65 years 70 years	29.248 26,891	0.12 0.11	245.827 254,726
Time horizon	5 years	10 years 25 years	53,330 87,445	0.20 0.25	269,810 351,089
Efficacy as per Deleu et al. synopsis[3]	29%	46%	24,624	0.20	120,241
Average daily dose from Deleu et al. (no wastage)[3]	15 mg per day	12.5 mg per day	23,363	0.12	195,871
Disease progression; "off" transitions derived from Lowin et al. (2011)[5]	After first cycle, same in both groups:[a] "Off" I to II: 0.2285 "Off" I to III: 0.0094 "Off" II to III: 0.1393 "Off" II to IV: 0.0032 "Off" III to IV: 0.0842	SoC group same as base case, apomorphine transitions halved:[a] "Off" I to II: 0.1206 "Off" I to III: 0.0023 "Off" II to III: 0.0718 "Off" II to IV: 0.0008 "Off" III to IV: 0.021	25,472	0.18	143,196
AE prevalence	As manufacturer's	Doubled Zero	29,550 28,876	0.10 0.14	295,086 211,963
Health care resource use	As manufacturer's	MRI and CT scans not included, nursing visit as per Findley et al.[9]	29,257	0.12	246,076
Base time awake	16 hours	14 hours 18 hours	27,566 30,733	0.14 0.11	202,264 282,529
Cost antiemetics	$0.054	$0	27,725	0.12	233,838
Mortality RR based on H&Y 4	3.858	4.99	28,891	0.12	250,342
Utilities derived from Walter and Odin	"Off" I: 0.489 "Off" II: 0.401 "Off" III: 0.313 "Off" IV: 0.225	"Off" I: 0.587 "Off" II: 0.0.507 "Off" III: 0.426 "Off" IV: 0.346	29,269	0.11	278,086
Hospitalization costs	OCCI 2011-2012 $17,893 (SD, $1,789)	OCCI 2015-2016 $15,521 (SD, $23,656)	30,399	0.12	253,970
Utilities, health care resource use, mortality based on H&Y 4	H&Y = 3.6	H&Y = 4.0	24,516	0.12	297,633

AE = adverse event; CDR = CADTH Common Drug Review; CT = computed tomography; H&Y = Hoehn and Yahr; ICUR = incremental cost-utility ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life-year; RR = relative risk; SD = standard deviation.

[a] "Off"-state transition probabilities were halved for the apomorphine group, and then both sets were converted from 6 months to 1 year using Eigen decomposition tool described in Chhatwal et al. (2016).[19]

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