CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Safinamide (Onstryv)

(Valeo Pharma Inc.)

Indication: For add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic Parkinson disease (PD) in patients experiencing "OFF" episodes while on a stable dose of levodopa. Safinamide has not been shown to be effective as monotherapy for the treatment of PD.

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Abbreviations

AE	adverse event
EQ-5D	EuroQol 5-Dimensions
H&Y	Hoehn and Yahr
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
MAO-B	monoamine oxidase B
PD	Parkinson's disease
QALY	quality-adjusted life-year
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Safinamide mesylate (Onstryv)
Study question	From the perspective of the Canadian publicly funded health care payer, what is the cost-effectiveness of safinamide as an adjunctive therapy to levodopa compared with the current standard of care for the treatment of patients with idiopathic Parkinson disease (PD) who are experiencing OFF episodes while on a stable dose of levodopa?
Type of economic evaluation	Cost-utility analysis
Target population	Patients with idiopathic PD who are experiencing OFF episodes while on a stable dose of levodopa.
Treatment	Safinamide mesylate, 50 mg or 100 mg oral tablet once daily as an adjunct to levodopa. The base-case analysis focused on 100 mg to align with the average daily dose used in the two pivotal studies (90 mg). The 50 mg dose was explored in a scenario analysis.
Outcome	QALYs
Comparators	• MAO-B inhibitors (as adjunct to levodopa): rasagiline, selegiline • COMT inhibitor (as adjunct to levodopa): entacapone • Dopamine agonists (as adjunct to levodopa): bromocriptine, pramipexole, ropinirole, rotigotine
Perspective	Canadian publicly funded health care payer.
Time horizon	10 years
Results for base case	In sequential analyses, safinamide 100 mg is dominated (i.e., more costly and fewer QALYs) by bromocriptine.
Key limitations	CADTH identified the following key limitations: • The time spent in OFF categories from month 24 were inappropriately applied to subsequent treatment cycles for the remainder of the time horizon. • Discontinuation due to a lack of efficacy was not included. • The applicability of AE data from short-term trials with unstratified safinamide dosing is uncertain. • More up-to-date health state utility values should have been applied in the economic model. • The impact of utility decrements for AEs is uncertain and an arbitrary utility decrement for worsening PD was applied, which likely overestimated the impact. • Relevant inputs were not modelled probabilistically.
CADTH estimate	• CADTH addressed these limitations, where possible, by incorporating probabilistic inputs, applying updated utilities from Kalabina et al., removing the worsening PD utility decrement, and applying long-term OFF transition probabilities. • Based on CADTH's base-case reanalyses, safinamide 100 mg remained dominated by bromocriptine, with both incremental costs and QALYs reduced in CADTH's base case compared with the sponsor's base case. The incremental differences in QALYs between treatments were minimal. If a decision-maker's willingness to pay is $100,000, a 95% reduction in the price of safinamide is required when using CADTH's base case, while a 70% reduction is required when using the sponsor's base case. • Key limitations with the model (not considering discontinuation due to a lack of efficacy or allowing testing of mean time spent in an OFF state) could not be addressed, and limitations with the sponsor's indirect treatment comparison (clinical heterogeneity and network sparsity) resulted in uncertainty of the cost-effectiveness estimates.

AE = adverse event; COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; PD = Parkinson disease; QALY = quality-adjusted life-year.

Drug	Safinamide mesylate (Onstryv)
Indication	For add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing "OFF" episodes while on a stable dose of levodopa. Safinamide has not been shown to be effective as monotherapy for the treatment of PD.
Reimbursement request	As per indication
Dosage form	Tablets, 50 mg and 100 mg safinamide (as safinamide mesylate), Oral
NOC date	January 10, 2019
Sponsor	Valeo Pharma Inc.

NOC = Notice of Compliance; PD = Parkinson disease.

Executive Summary

Background

Safinamide mesylate is a monoamine oxidase B (MAO-B) inhibitor used as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic Parkinson disease (PD) in patients experiencing OFF episodes while on a stable dose of levodopa.[1] It is available as 50 mg and 100 mg tablets at a submitted price of $6.90 per tablet, regardless of strength.[2] The recommended starting dose of safinamide is 50 mg daily, which may be increased to 100 mg daily after two weeks based on clinical need and tolerability.[1]

The sponsor submitted a cost-utility analysis comparing safinamide 100 mg with multiple comparators that included MAO-B inhibitors (rasagiline, selegiline), catechol-O-methyltransferase inhibitors (entacapone), and dopamine agonists (bromocriptine, pramipexole, ropinirole, rotigotine) as adjunct therapies to levodopa.[2] The sponsor's base case was a probabilistic analysis conducted from the perspective of a Canadian publicly funded health care payer over a 10-year time horizon, with costs and benefits discounted at a rate of 1.5% per annum. The model consisted of 18 mutually exclusive health states: 16 base health states were based on four categories of waking time spent in an OFF state applied to four Hoehn and Yahr (H&Y) stages (stages 2 to 5) and the remaining two health states were discontinuation due to adverse events (AEs) followed by a treatment switch, and death. Patients on safinamide or a comparator could experience one of six scenarios every six months:

- transition to more time spent in an OFF state but not progress on the H&Y scale
- progress on the H&Y scale but maintain time spent in an OFF state
- progress on both the H&Y scale and time spent in an OFF state
- maintain the current health state
- discontinue treatment due to AE while in any health state and switch treatment
- enter death from any health state.

Treatment effects and probabilities of AEs were based on a sponsor-commissioned unpublished indirect treatment comparison (ITC). Pooled results for OFF time were derived for both the 50 mg and 100 mg doses of safinamide. Relative risks of AEs for comparators

versus safinamide 50 mg or 100 mg were applied in the model. It was assumed by the sponsor that OFF time would remain constant beyond 24 months based on data from studies 016 and 018. Patients could transition to worse H&Y stages due to the natural progression of the disease, based on probabilities identified in published literature. Patients who discontinued treatment due to AEs were assumed to switch to an alternate adjuvant of a different treatment class and incur the costs of the new adjuvant. Due to a lack of available data, the sponsor assumed subsequent adjuvant treatments to have the same efficacy as safinamide 100 mg. Unless patients died or discontinued due to AEs, patients remained on the original treatment throughout the modelled time horizon. Utility estimates for each of the OFF health states varied according to H&Y stage. Drug-acquisition costs for safinamide were submitted by the sponsor and comparator drug costs were obtained from the Ontario Drug Benefit[3] or Saskatchewan Drug Plan[4] formularies.

In the sponsor's base case, safinamide 100 mg was dominated by bromocriptine, i.e., safinamide was associated with greater costs and fewer quality-adjusted life-years (QALYs), as the acquisition cost of safinamide was higher, duration of treatment was longer and, according to the ITC, [redacted]. In the sponsor's scenario analyses, safinamide 50 mg was also dominated by bromocriptine.

Summary of Identified Limitations and Key Results

CADTH identified several limitations in the economic model submitted by the sponsor. The sponsor inappropriately applied time spent in OFF categories from month 24 to subsequent treatment cycles for the remainder of the time horizon. This assumes no waning of treatment effect and that patients would only transition between the 16 base health states according to natural disease progression (i.e., H&Y stages). Transition probabilities according to time spent in OFF categories were available from the published literature and could have been used rather than the simplifying assumption.

The sponsor only included treatment discontinuations due to AEs. However, the clinical expert consulted by CADTH indicated that some patients may not discontinue treatment due to AEs, as they are more willing to tolerate these symptoms with the aim of continuing treatment and receiving the associated benefits, given the disease severity. In addition, patients are also likely to discontinue treatment due to a perceived lack of efficacy.

The applicability of data from Study 016[5] and SETTLE[6] to inform rates of AEs for the model time horizon is uncertain, as longer-term data from an 18-month (total 24 months) extension study of safinamide was also available. This data may better align with the expected long-term AEs associated with safinamide and provide a sufficient period of time for less frequent AEs to emerge. Additionally, the SETTLE trial did not report results stratified according to the dose of safinamide (i.e., 50 mg and 100 mg); therefore, it is uncertain how applicable AE probabilities from this trial would be to each safinamide dose.

Additional limitations included identification of alternate utility values from the literature. Also, feedback from the clinical expert consulted by CADTH suggested the utility decrements associated with some AEs were overestimated or led to double counting in the impact of treatments, as worsening PD would already be captured as part of the 16 base health state utilities according to time spent in OFF and H&Y stage. Relevant parameters (hazard ratio for PD mortality, mean time spent in OFF state) were not assessed probabilistically. The CADTH clinical review also identified limitations with the ITC that resulted in uncertainty in

the comparative effectiveness, although it was noted that the sponsor-submitted [redacted].

The CADTH base case reflected changes to the following parameters: correction of probabilistic inputs; applying updated utilities from Kalabina et al.; removal of the worsening PD utility decrement; and application of long-term OFF transition probabilities. CADTH was unable to test the impact of the lack of evidence on the long-term effectiveness of safinamide or discontinuation due to a lack of efficacy, nor test alternate assumptions regarding the mean time spent in OFF for safinamide. In the CADTH reanalyses, safinamide (at either dose) remained dominated by other available treatments, i.e., safinamide was associated with greater costs and fewer QALYs. Specifically, safinamide 50 mg was dominated by bromocriptine, entacapone, and rasagiline, while safinamide 100 mg was dominated by bromocriptine. The result was driven by the duration of treatment with each adjunct medication, ranging from 2.93 years for bromocriptine to 7.71 years for selegiline (4.85 years for safinamide), leading to differences in the discontinuation rates for treatments.

Conclusions

In line with the sponsor's submitted base case, CADTH found that both safinamide 50 mg and 100 mg were dominated by other treatments for PD. If a decision-maker's willingness-to-pay (WTP) threshold is $100,000 per QALY, a price reduction of approximately 95% is required for safinamide 100 mg to be considered cost-effective. However, several limitations were identified that could not be addressed in the submitted model, most notably the exclusion of discontinuation due to lack of efficacy. In line with the findings of the economic evaluation, the results of the sponsor's [redacted]. As such, the true cost-effectiveness of safinamide is uncertain.

Information on the Pharmacoeconomic Submission

Summary of Sponsor's Pharmacoeconomic Submission

Overview

The sponsor submitted a cost-utility analysis using a cohort-based Markov model over a 10-year time horizon from the perspective of the Canadian publicly funded health care payer.[2] Safinamide was compared with multiple treatments which included MAO-B inhibitors (rasagiline, selegiline), catechol-O-methyltransferase inhibitors (entacapone), and dopamine agonists (bromocriptine, pramipexole, ropinirole, rotigotine).[2] The sponsor focused on safinamide 100 mg as the primary intervention, as the majority of patients (90.9%) were receiving 100 mg per day in the SETTLE study.[6] The perspective was that of the Canadian publicly funded health care payer, with a 10-year time horizon. The base case was a probabilistic analysis of 5,000 simulations with six-month cycles. Costs and benefits were discounted at an annual rate of 1.5%.

Model Structure

The characteristics of the model population were based on a sponsor-conducted double-blind 24-week randomized placebo-controlled trial (study 016).[5] The model consisted of 18 mutually exclusive health states; 16 base health states were divided into four categories of waking time (16 hours) spent in an OFF state (e.g., 0% to 25%, 25% to 50%, etc.) according to H&Y stage, which measures symptomatic progression of PD (i.e., four OFF time categories in each of the four H&Y stages). The remaining two health states were discontinuation due to AEs followed by a treatment switch, and death. Patients entered the model in one of the 16 base health states (Figure 1). Patients on safinamide or a comparator could experience one of six scenarios every six months:

- transition to more time spent in an OFF state but not progress on the H&Y scale
- progress on the H&Y scale but maintain time spent in an OFF state
- progress on both the H&Y scale and time spent in an OFF state
- maintain the current health state
- discontinue treatment due to AE while in any health state and switch treatment
- enter death from any health state.

Model Input: Baseline Characteristics

The initial distribution of patients within the base health states was derived from Study 016[5] using the mean baseline hours spent in OFF prior to treatment and the corresponding H&Y stage (excluding H&Y stage 1, as these patients were assumed to not receive adjunctive treatment). Based on this distribution, the majority of patients in the sponsor's model were assumed to have a disease severity score of H&Y stage 2 (47.0%) or H&Y stage 3 (39.0%), and few patients had a H&Y stage 4 score (14.0%). Additionally, most patients were in either the OFF 1 or OFF 2 health states (31.5% and 59.06%, respectively) and the remaining patients entered the model in either OFF 3 (8.54%) or OFF 4 (0.90%) health state at treatment initiation. The mean age at model entry was 60 years and 72% of patients were male. Patients were assumed to be awake for 16 hours per day.

Model Input: Treatment Effectiveness, AEs, and Death

Model inputs for disease progression rates were obtained from a published economic evaluation assessing the economic impact of slowing PD, which used data identified in a systematic literature review of longitudinal studies investigating H&Y progression rates.[7]

The change in total OFF time per day was derived from an unpublished ITC provided by the sponsor comparing safinamide 50 mg and 100 mg with placebo and the relevant comparators of interest (see Table 25 of the CADTH Common Drug Review [CDR] Clinical Report). Due to the lack of long-term data for change in total OFF time (24 months for safinamide from studies 016 and 018, six months for comparators), the sponsor assumed OFF time is maintained beyond 24 months and applied the OFF categories at 24 months for the remainder of the time horizon. Transitioning from one OFF category to another was independent of H&Y stage progression probabilities. To determine the total proportion of patients within each of the 16 base health states per cycle, the probability of being in any particular OFF category was multiplied by the corresponding H&Y stage probability. The relative risk of treatment-related AEs and discontinuations due to AEs were also derived using the ITC and applied directly in the model for the duration of treatment (Table 10). For relative risks where data were unavailable, probabilities were set to equal a comparator from the same treatment class. Patients who discontinued treatment were assumed to switch to an alternate adjuvant from a different treatment class and incur the costs of the new adjuvant treatment. Additionally, due to a lack of available data, the sponsor assumed subsequent adjuvant treatments to have the same efficacy as safinamide 100 mg.

Mortality was based on Statistics Canada (2017)[8] life tables and adjusted based on the hazard ratio of death for patients with PD reported in Jones et al. (2012).[9]

Model Input: Utilities

Utility estimates were obtained from Lowin et al. (2017)[10] and varied according to time spent in OFF and H&Y stage for the 16 base health states, as shown in Table 11. Lowin et al. utilized EuroQol 5-Dimensions (EQ-5D) data derived from the Adelphi Disease Specific Programme,[11] patient-level data from a published clinical study,[12] and data from DAPHNE (Duodopa in Advanced Parkinson's: Health Outcomes & Net Impact, NCT00141518)[13] and GLORIA.[12]

Utility decrements were applied for all AEs included in the model and were obtained from the following sources: Sullivan et al. (2004),[14] a cost-utility analysis in depression; the CADTH Movapo review,[15] derived using Walter and Odin (2015);[16] clinical expert opinion; or sponsor assumptions. The majority of AE utility decrements (i.e., worsening PD, headache, nausea, constipation, somnolence, insomnia, and hallucination) were defined by the sponsor's clinical experts as chronic events due to the lack of effective treatment options and applied over the entire six-month cycle. Acute events (i.e., dizziness/hypotension and postural hypotension) could be readily treated and were expected to persist for two months per six-month cycle. An overview of the utility decrements is shown in Table 12.

Model Input: Health Care Resource Utilization and Costs

Health care utilization was assumed to vary between the base health states according to total time spent in OFF states and H&Y stages. Utilization associated with emergency room visits, hospitalizations, professional visits (i.e., by nurses, general practitioners, neurologists, and psychiatrists), and monitoring tests (i.e., magnetic resonance imaging and computed

tomography) were based on a cross-sectional study by Findley et al. (2011) conducted in the UK.[17] Additionally, clinical experts provided estimates for resource use not identified by Findley et al. (2011)[17] and modified the utilization rates to be more reflective of Canadian practice (Table 13). The sponsor estimated the costs (direct and non-direct) associated with each health state in the model as well as PD treatment costs and AE management costs. Hospitalization costs were obtained from the Canadian Institute for Health Information, emergency room costs from the Ontario Case Costing Initiative,[18] professional visit costs from the Ontario Schedule of Benefits for Physician Services,[19] and monitoring test costs from the Ontario Schedule of Benefits for Laboratory Services.[20] Safinamide drug-acquisition costs were based on the sponsor's submitted price of $6.90 per tablet, regardless of strength, and comparator costs were obtained from the Ontario Drug Benefit[3] or Saskatchewan Drug Plan[4] formularies. The average daily dose of safinamide was obtained from the SETTLE trial and all comparators from the sponsor's ITC.

Sponsor's Base Case

In the base-case analysis, the sponsor reported that over a 10-year time horizon, the total costs for safinamide 100 mg were higher (+$1,300 to $16,400) than the costs for all comparators except rotigotine (−$7,300), while the total QALYs were greater than all comparators except bromocriptine. The sponsor's sequential analyses reported that only selegiline, entacapone, and bromocriptine were on the cost-effectiveness efficiency frontier. Of those treatments, selegiline had the lowest costs and QALYs followed by entacapone and bromocriptine. The resulting sequential incremental cost-utility ratio (ICUR) was $80,054 per QALY for entacapone compared with selegiline and $107,521 per QALY for bromocriptine compared with entacapone. Safinamide was dominated by bromocriptine (Table 2). The sponsor noted that no difference in total life-years was found between treatment arms. At a WTP threshold of $50,000 and $100,000 per QALY, the probability of safinamide 100 mg being cost-effective was reported to be 0%.

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

Treatment	Total costs ($)	Total QALYs	Pairwise ICUR versus safinamide ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated strategies				
Selegiline	137,025	3.900	136,620	–
Entacapone	146,354	4.016	1,846,797	80,054
Bromocriptine	152,103	4.070	Dominates safinamide	107,521
Dominated strategies				
Pramipexole	140,776	3.831	67,027	Dominated by selegiline
Rasagiline	149,050	3.986	130,583	Dominated by entacapone
Ropinirole	143,062	3.732	36,144	Dominated by selegiline
Rotigotine	160,842	3.914	Dominated by safinamide	Dominated by entacapone and bromocriptine
Safinamide 100 mg	**153,473**	**4.020**	**–**	**Dominated by bromocriptine**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted probabilistic scenario analyses varying discount rate, time horizon, societal perspective, AEs, duration of long-term OFF extrapolations, daily awake hours, and use of safinamide 50 mg dosing. The results of the scenario analyses were aligned with the sponsor's base case, as safinamide was dominated in all scenarios; the results of the analysis of safinamide 50 mg are reported in Table 16.

Limitations of Sponsor's Submission

- **Uncertainty in the long-term extrapolation of data:** The sponsor inappropriately applied time spent in OFF categories from month 24 to subsequent treatment cycles for the remainder of the time horizon. This assumes no waning of treatment effect will occur and patients would only transition between the base health states according to natural disease progression (i.e., H&Y stages). This would bias results in favour of safinamide when compared with less efficacious treatments due to the reduced time spent in OFF being maintained for the remainder of the time horizon. The clinical expert consulted by CADTH considered this assumption to be unreasonable, as patients are likely to regress while on treatment and experience an increase in the total time spent in OFF within the 10-year time horizon. As part of the pharmacoeconomic submission, the sponsor explored extrapolating the data beyond 24 months using a Weibull or log-normal distribution; however, a continued benefit over time was observed and was not considered clinically feasible by the sponsor's clinical experts (results not presented).

  To explore the impact of waning treatment effect, the transition probabilities between OFF time categories reported by Kalabina et al. (2019)[21] and Lowin et al. (2017),[10] which were derived from Palmer et al. (2002),[22] were incorporated into CADTH's base-case reanalyses and applied beyond month 24 (Table 17). This approach is more likely to be representative of the current clinical setting for PD patients, as the clinical expert consulted by CADTH indicated that it is highly unlikely that patients would maintain time spent in OFF as they progress to a more advanced disease state.

  The sponsor's assumption that subsequent adjuvant therapies have the same efficacy as safinamide may overestimate the benefits of safinamide, [redacted].

- **Discontinuation due to lack of efficacy not considered:** The clinical expert consulted by CADTH indicated that patients are likely to discontinue treatment due to a perceived lack of efficacy. Additionally, the clinical expert estimated that approximately 60% of treatment discontinuations would be due to a lack of efficacy.

  The sponsor included discontinuations due to AEs in the economic model; however, the clinical expert consulted by CADTH highlighted that most AEs, with the exception of dyskinesia, could be clinically managed to ensure patients remain on treatment. Based on the structural limitations of the economic model, CADTH could not explore the impact of treatment discontinuation due to a lack of efficacy. Given the impact that the duration of adjunct medication has on the total cost of treatment and the small incremental differences in cost, this likely has implications on the cost-effectiveness of safinamide.

- **Information on AEs is associated with uncertainty:** In the sponsor's ITC, data from Study 016[5] and SETTLE[6] were included as part of the analyses to align with the duration of trials (24 weeks) for comparator treatments; however, longer-term data from an 18-month (24 months total) extension study of safinamide were also available, as were longer-term data for other comparator treatments. Data from the extension study may better align with the expected long-term AEs associated with safinamide and provide a sufficient period of time for less frequent AEs to be identified. Additionally, the short-term SETTLE trial did not report results stratified according to the dose of safinamide (i.e., 50 mg and 100 mg); therefore, it is uncertain how applicable AE probabilities from this trial would be to each safinamide dose individually.

  The clinical expert consulted by CADTH also highlighted that due to patient heterogeneity, some AEs may become more tolerable with extended exposure and the impact on tolerability and quality of life varies by patient. To assess the impact of AEs, CADTH limited the AEs to the first treatment cycle as part of a scenario analysis.

- **Health state utility values:** In the sponsor's base case, utility estimates were obtained from Lowin et al. (2017),[10] who conducted a generalized estimating equation regression analysis using data from four clinical studies to derive utilities based on time spent in OFF and H&Y stage.[11-13,23] However, a more recent study by Kalabina et al. (2019)[21] also provides utility estimates according to OFF and H&Y stage. As these publications are studying the same intervention (levodopa/carbidopa intestinal gel) and patient population (advanced PD), CADTH considered Kalabina et al. to be a more appropriate source of utilities as part of the base case. The utility estimates reported by Lowin et al. were explored as part of a scenario analysis.

- **AE utility decrement:** A utility decrement for hallucination was not reported in the publication by Sullivan et al. (2004)[14] and, therefore, the sponsor applied a weighted average of all AEs as a proxy value. CADTH considered this to be a non-conservative approach, as the weighted average utility decrement (0.085) is higher than other AEs reported by the sponsor (i.e., nausea and constipation) and there were substantial differences between safinamide and relevant comparators for hallucination, favouring safinamide. Additionally, the clinical expert consulted by CADTH highlighted that patients experiencing hallucinations would receive additional medication to manage these symptoms and the impact on quality of life was expected to be manageable.

  The sponsor also assumed a 10% EQ-5D decrement would be proportionately applied to the overall QALYs for patients experiencing worsening PD due to treatment-related AEs. However, since the sponsor considered worsening PD to be a chronic event and applied a decrement for the duration of treatment, this is likely captured as part of the natural disease progression utilities for the base health states according to H&Y stage and time spent in OFF.[10] This would result in a double counting of the EQ-5D decrement due to worsening PD in the economic model; therefore, this utility decrement was removed as part of CADTH's base-case reanalyses.

- **Relevant inputs were not tested probabilistically:** In the sponsor's economic model, the hazard ratio for PD-related mortality and mean time spent in OFF for safinamide 50 mg and 100 mg were not included as probabilistic inputs. As part of best practice and in alignment with CADTH's Guidelines for the Economic Evaluation of Health Technologies: Canada,[24] uncertainty in parameter values should be captured probabilistically in the base case. Therefore, in CADTH's base case, the hazard ratio for

PD-related mortality was incorporated using a log-normal distribution; however, the mean time spent in OFF for safinamide 50 mg and 100 mg could not be addressed.

CDR Reanalyses

The CADTH reanalyses did not address the following limitations: lack of evidence on long-term effectiveness of safinamide, discontinuation due to a lack of efficacy, and mean time spent in OFF for safinamide.

CADTH's reanalyses included the following changes to the sponsor's base case:

1. Correction: Incorporated the hazard ratio for PD-related mortality within the probabilistic analysis.
2. Application of utilities according to H&Y stage and time spent in OFF from Kalabina et al. (2019).[21]
3. Removal of utility decrement due to worsening PD.
4. Long-term extrapolation of OFF using transition probabilities as reported by Kalabina et al. (2019)[21] and Lowin et al. (2017),[10] as derived from Palmer et al. (2002).[22]
5. **CADTH base case (1 + 2 + 3 + 4).**

CADTH's base-case results, including dominated strategies, are presented in Table 3. Additional summary information of the results and cost breakdowns are presented in Table 18 and Table 19.

Based on CADTH's reanalyses, safinamide 100 mg was dominated (i.e., associated with greater costs and fewer QALYs) by bromocriptine. Only selegiline and bromocriptine were considered cost-effective for safinamide 100 mg.

Table 3: CADTH Base Case Results – Safinamide 100 mg

Description	Treatment	Total costs ($)	Total QALYs	Pairwise ICUR versus safinamide ($/QALY)	Sequential ICUR ($/QALY)
CADTH base case (1 + 2 + 3 + 4)	**Non-dominated strategies**				
	Selegiline	153,823	3.680	282,611	–
	Bromocriptine	167,373	3.789	Dominates safinamide	123,612
	Dominated strategies				
	Entacapone	161,350	3.732	253,531,817	Extendedly dominated by bromocriptine
	Pramipexole	156,815	3.575	75,632	Dominated by selegiline
	Rasagiline	164,050	3.707	180,908	Dominated by entacapone
	Ropinirole	158,480	3.481	40,709	Dominated by selegiline
	Rotigotine	176,684	3.647	Dominated by safinamide	Dominated by bromocriptine and entacapone
	Safinamide 100 mg	**168,725**	**3.732**	**–**	**Dominated by bromocriptine**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

The impact of safinamide 50 mg was also explored using CADTH reanalyses 1 to 4. Results are shown in Table 20. When using CADTH reanalyses, safinamide 50 mg was dominated.

Scenario analyses using the CADTH base case included the following:

5a. Vary patient entry age (65 years) and proportion of male patients (60%).

5b. Vary base time spent awake (14 and 18 hours per day).

5c. Apply AEs only during the first cycle.

5d. Apply utilities according to H&Y stage and time spent in OFF from Lowin et al. (2017).[10]

5e. Analyze subsequent treatment efficacy using entacapone and selegiline.

5f. Remove costs and utilities for subsequent treatment.

Safinamide 100 mg was dominated in all of CADTH's scenario analyses. Detailed cost information can be found in Table 21.

Price Reduction Analyses

Price reduction analyses were undertaken based on both the CADTH and sponsor base case for the comparison of safinamide versus the comparators of interest.

Based on CADTH's base-case reanalyses, a price reduction of approximately 95% would be required for safinamide 100 mg to be considered cost-effective if a decision-maker's WTP is $100,000 per QALY while, based on the sponsor's base case, a price reduction of approximately 70% would be required for safinamide 100 mg to be considered cost-effective (Table 4). Using CADTH's base case, a 99.9% price reduction for safinamide was explored that resulted in an ICUR of $85,797 per QALY; therefore, if a decision-maker's WTP is $50,000 per QALY, safinamide is not considered cost-effective. When using the sponsor's base case, a 99% reduction is required for safinamide to be cost-effective.

Table 4: CADTH Sequential Reanalyses – Price Reduction Scenarios

Price	Safinamide price per unit ($)	Safinamide 100 mg	
		Sponsor base case ICUR ($/QALY)	CADTH base case ICUR ($/QALY)
Submitted	6.90	If λ < 80,054: Selegiline If 80,054 < λ < 107,521: Entacapone If λ > 107,521: Bromocriptine	If λ < 123,612: Selegiline If λ > 123,612: Bromocriptine
70% reduction	2.07	If λ < 75,706: Selegiline If 75,706 < λ < 121,613: Safinamide 100 mg If λ > 121,613: Bromocriptine	If λ < 123,110: Selegiline If λ > 123,110: Bromocriptine
95% reduction	0.35	If λ < 54,713: Selegiline If 54,713 < λ < 172,247: Safinamide 100 mg If λ > 172,247: Bromocriptine	If λ < 96,123: Selegiline If 96,123 < λ < 149,535: Safinamide 100 mg If λ > 149,535: Bromocriptine

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; λ = willingness to pay.

Issues for Consideration

Complexity of dosing regimens: The complex dosing schedule of levodopa and other PD therapies makes receiving and adhering to treatment difficult for PD patients and caregivers (see Patient Input). Patients and caregivers may find it easier to follow adjunctive medications that are taken once daily (e.g., safinamide, rotigotine, rasagiline) or twice daily (e.g., selegiline) compared with those with more complex daily dosing (e.g., pramipexole,

ropinirole, entacapone, bromocriptine). This may potentially increase adherence and, consequently, the effects of treatment in a real-world setting.

Contraindication with antidepressants: Serotonin syndrome is a major health concern for both physicians and patients, as severe central nervous system toxicity associated with hyperpyrexia and death has been reported in patients receiving antidepressant medication (i.e., selective serotonin reuptake inhibitors [SSRIs]; selective serotonin-norepinephrine reuptake inhibitors [SNRIs]; and tricyclic or tetracyclic antidepressants [TCAs]) combined with MAO-B inhibitors (i.e., selegiline, rasagiline, safinamide).[1,25,26] Based on the findings from Singian et al. (2016),[27] 38.1% of patients with PD are diagnosed with depression as a comorbid condition, with females having a higher prevalence compared with males (42.8% versus 34.2%; $P < 0.05$). Additionally, the majority of PD patients were receiving SSRIs (52.2%); however, patients also received SNRIs (17.1%) and TCAs (9.9%). Treatments that are not restricted by an antidepressant contraindication may be seen as more favourable, given the proportion of PD patients with depression comorbidities.

Amantadine off-label usage: Canadian guidelines for PD and the clinical expert consulted by CADTH highlight the off-label usage of amantadine as a potential comparator (level D evidence) for Canadian patients; however, this should not be considered a drug of first choice.[28] Currently, amantadine is prescribed to improve dyskinesia due to motor fluctuations (level C evidence). As amantadine was not included as part of the sponsor's ITC, comparative effectiveness and safety could not be determined; therefore, amantadine was not explored as part of CADTH's reanalyses.

Patient Input

Input was received by two patient groups: Parkinson Canada and Parkinson Society British Columbia. Respondents with PD from both patient groups indicated having anxiety, stress, loss of confidence, and sadness as the most common emotional impact of the disease. Physical changes included impaired balance, muscle rigidity, and slowness of movement.

According to Parkinson Canada, 67% of respondents with PD have experienced side effects when taking medications, including disturbed sleep, nausea, constipation, dyskinesia, fatigue, and hallucinations. Furthermore, 14% of respondents reported difficulties in receiving treatment, including: swallowing, remembering to take medication, and timing their medication with meals. Patients reported the need for a medication that would cure the disease, or stop disease progression, and effectively control symptoms. There is also an expressed need for longer-lasting medications that limit or eliminate OFF times with fewer side effects.

The sponsor's economic submission incorporated the impact of AEs, disease progression, and physical changes according to H&Y stage and time spent in OFF as part of the analyses.

Conclusions

CADTH identified several limitations in the sponsor's submitted analysis, such as the lack of long-term effectiveness evidence for safinamide and structural issues with the model (not considering discontinuation due to a lack of efficacy or allowing testing of mean time spent in an OFF state), which could not be addressed. Other limitations, such as correcting model inputs to be sampled probabilistically, applying appropriate utilities, removing the worsening PD utility decrement due to potential double counting, and applying long-term OFF transition probabilities, were considered in the CADTH base case.

CADTH found, in line with the sponsor's submission, that safinamide 100 mg was dominated by bromocriptine, i.e., it was associated with greater costs and fewer QALYs. Based on CADTH's base-case reanalyses, if a decision-maker's WTP threshold is $100,000 per QALY, a price reduction of approximately 95% is required for safinamide 100 mg to be considered cost-effective. If a decision-maker's WTP is $50,000 per QALY, safinamide is not considered cost-effective in CADTH's base case.

Several limitations were identified that could not be addressed in the submitted model, most notably the exclusion of discontinuation due to lack of efficacy. In line with the findings of the economic evaluation, [redacted]. As such, the true cost-effectiveness of safinamide is uncertain.

Appendix 1: Cost Comparison

The comparators presented in the 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 sponsor list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 5: CADTH Common Drug Review Cost Comparison Table for Parkinson Disease

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Safinamide (Onstryv)	**50 mg 100 mg**	**Tablet**	**6.9000**	**50 mg to 100 mg daily[a]**	**6.90**	**2,520**
Dopamine agonists						
Bromocriptine (generics)	2.5 mg 5 mg	Tablet Capsule	1.0188 1.5251	2.5 to 40 mg daily, in two to three doses[b]	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[c] 0.3901 0.3901	1.5 mg to 4.5 mg in three equal doses[b]	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 three equal doses[b]	0.85 to 3.75	311 to 1,367
Rotigotine (Neupro)	2 mg / 24 h 4 mg / 24 h 6 mg / 24 h 8 mg / 24 h	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
Oral levodopa/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 five to six doses[b]	4.42 to 5.22	1,614 to 1,937
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 three to four 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 two to four daily doses	0.71 to 5.69	260 to 2,078
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

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
MAO-B inhibitors						
Rasagiline (generics)	0.5 mg 1 mg	Tablet	6.1285 6.1285	0.5 to 1 mg daily	6.13	2,237
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

COMT = catechol-O-methyltransferase; h = hour; MAO-B = monoamine oxidase B.

All prices are from the Ontario Drug Benefit Formulary (accessed August 2019)[3] unless otherwise indicated and do not include dispensing fees. Annual costs are based on 365.25 days per year.

[a] Sponsor's submitted price.[2]

[b] Represents the recommended maintenance dose as per the sponsor's product monograph.

[c] Saskatchewan formulary (accessed August 2019).[4]

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Safinamide 100 mg Relative to All Comparators (CDR Reanalyses)?

Safinamide versus all comparators	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes				X		
Quality of life			X			
ICUR or net benefit calculation	CADTH base case: Safinamide 100 mg was dominated.					

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NA = not applicable.

Appendix 3: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	24-week AE probabilities from Study 016 were reported to be converted to 6-month probabilities; however, the sponsor incorrectly converted these probabilities using a 2-year duration.		
Was the material included (content) sufficient?			X
Comments	Assumptions regarding AE probabilities were not explained in the sponsor's submission and discrepancies between the ITC and PE reports were identified. Multiple requests for additional information and clarification were sent to the sponsor regarding how discontinuation and AE probabilities were derived.		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

AE = adverse event; ITC = indirect treatment comparison; PE = pharmacoeconomic.

Table 8: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

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

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

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

☐ 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	

Appendix 4: Summary of Other Health Technology Agency Reviews of Drug

Safinamide has been reviewed and recommended by Australia's Pharmaceutical Benefits Advisory Committee (PBAC)[29] and France's Haute Autorité Santé (HAS)[30] for combination therapy with levodopa for idiopathic PD patients with mid- to late-stage disease. The recommendation by HAS was based on a moderate benefit of safinamide for daily ON time; however, no clinical value was added when compared with other PD treatments. No economic assessment was published.

Details of the review by PBAC are presented below in Table 9.

Table 9: Other Health Technology Agency Findings

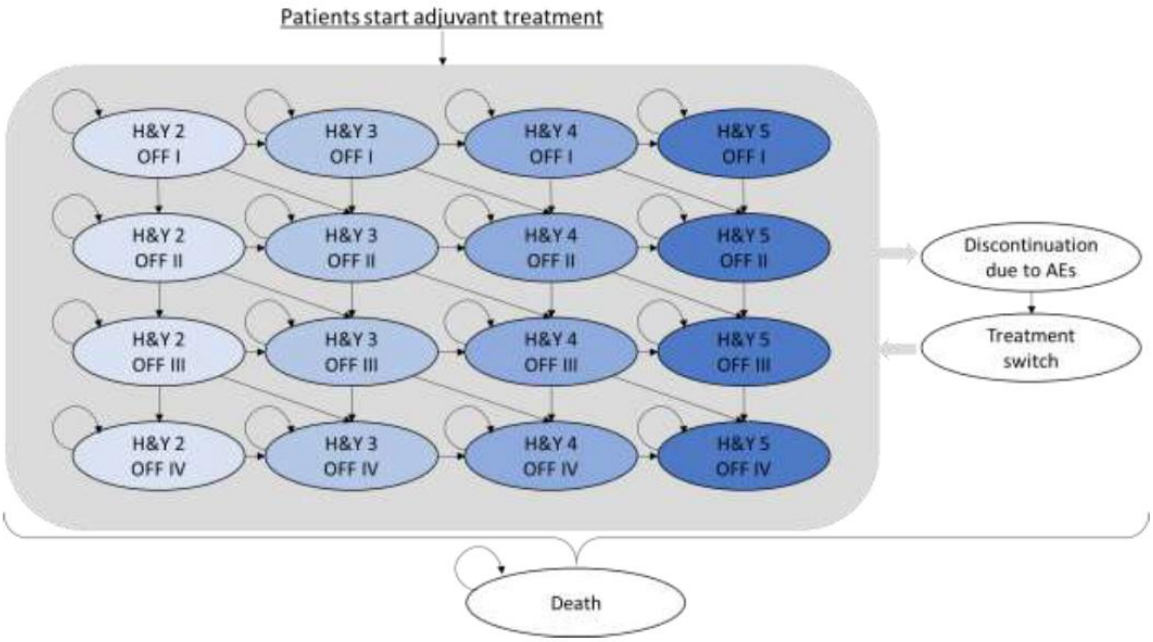
	PBAC (November 2018)[29]
Treatment	Safinamide 50 mg and 100 mg tablet administered once per day.
Price	Redacted.
Similarities with CDR submission	Outcomes of interest; same indication.
Differences with CDR submission	Cost-minimization analysis compared only with rasagiline using an ITC.
Sponsor's results	Redacted.
Issues noted by the review group	Steady-state dosing not implemented, incorrect submission price of comparator used, noninferior claim for comparative effectiveness for the 50 mg dose was not adequately supported by data.
Results of reanalyses by the review group	Redacted.
Recommendation	Accepted for restricted benefit of adult patients with fluctuating idiopathic PD as an add-on therapy to a regimen that includes levodopa.

CDR = CADTH Common Drug Review; ITC = indirect treatment comparison; PBAC = Pharmaceutical Benefits Advisory Committee; PD = Parkinson disease.

Appendix 5: Reviewer Worksheets

Model Structure

Figure 1: Model Structure Overview



AE = adverse event; H&Y = Hoehn and Yahr.

Note: OFF I = OFF 1; OFF II = OFF 2; OFF III = OFF 3; OFF IV = OFF 4.

Source: Sponsor's pharmacoeconomic submission.[2]

Model Inputs

Treatment Effectiveness and AEs

Table 10: Probability of Discontinuation per Six-Month Cycle

Treatment	Probability for safinamide 50 mg	Probability for safinamide 100 mg
Bromocriptine	0.137	0.161
Entacapone	0.083	0.100
Pramipexole	0.061	0.075
Rasagiline	0.064	0.078
Ropinirole	0.052	0.062
Rotigotine	0.048	0.059
Safinamide 50 mg	0.053	0.064
Safinamide 100 mg	0.068	0.082
Selegiline	0.022	0.026

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

Health State Utilities

Table 11: Health State Utility Values (EuroQol 5-Dimensions)

Health state	H&Y 2	H&Y 3	H&Y 4	H&Y 5
OFF 1	0.676	0.566	0.456	0.347
OFF 2	0.646	0.536	0.426	0.316
OFF 3	0.615	0.506	0.396	0.286
OFF 4	0.585	0.475	0.366	0.256

H&Y = Hoehn and Yahr.

Source: Adapted from the sponsor's pharmacoeconomic submission[2] and Lowin et al. (2017).[10]

Table 12: Adverse Event Utility Decrements (EuroQol 5-Dimensions) and Health Care Cost

Adverse event	Resource use	Duration of AE	Utility decrement per 6-month cycle	AE unit cost ($)	Source for unit cost
Worsening PD	One specialist visit	6 months	−10%	100.62	Ontario SoB:[19] A185
Dizziness/hypotension	One GP visit	2 months	−0.053	77.20	Ontario SoB:[19] A005
Dyskinesia	One specialist visit	6 months	−0.330	100.62	Ontario SoB:[19] A185
Headache	One specialist visit	6 months	−0.115	100.62	Ontario SoB:[19] A185
Postural hypotension	–	2 months	−0.053	–	–
Nausea	One GP visit, domperidone 10 mg for 2 months	6 months	−0.065	64.12	Ontario SoB:[19] A005; ODB Formulary[3]
Constipation	One GP visit	6 months	−0.065	77.20	Ontario SoB:[19] A005
Somnolence	One GP visit	6 months	−0.085	77.20	Ontario SoB:[19] A005
Insomnia	One GP visit	6 months	−0.129	77.20	Ontario SoB:[19] A005
Hallucination	One specialist visit, quetiapine 100 mg for 2 months	6 months	−0.085	108.53	Ontario SoB:[19] A185; ODB Formulary[3]

AE = adverse event; GP = general practitioner; ODB = Ontario Drug Benefit; PD = Parkinson disease; SoB = Schedule of Benefits.

Source: Adapted from the sponsor's pharmacoeconomic submission,[2] CADTH Movapo Report,[15] and Sullivan et al. (2004).[14]

Health Resource Utilization and Costs

Table 13: Health Care Resource Use and Unit Costs Applied in the Model by OFF and H&Y Health States per Six-Month Cycle

Health State		ER visits	Hosp.	Neur. visits	GP visits	Nurse visits	Psych. visits	MRI	CT
OFF	H&Y								
1	2	0.07	0.04	1.86	0.54	1.20	0.93	0.18	0.11
	3	0.23	0.12	1.43	1.45	1.17	0.71	0.12	0.15
	4	0.49	0.25	1.47	1.69	1.67	0.74	0.13	0.19
	5	0.60	0.30	0.80	2.94	1.38	0.40	0.04	0.24
2	2	0.07	0.03	0.81	1.91	1.43	0.40	0.15	0.10
	3	0.38	0.19	1.48	1.80	1.78	0.74	0.19	0.17
	4	0.46	0.23	1.36	2.10	1.96	0.68	0.23	0.29
	5	0.89	0.45	2.43	1.79	2.40	1.22	0.28	0.34
3	2	0.50	0.25	0.06	1.42	0.00	0.03	0.22	0.19
	3	0.50	0.25	1.00	1.75	1.50	0.50	0.25	0.25
	4	0.83	0.42	1.67	2.09	2.00	0.83	0.34	0.25
	5	0.67	0.34	2.75	2.42	4.75	1.38	0.34	0.34
4	2	0.72	0.36	0.37	2.16	1.01	0.19	0.22	0.22
	3	0.64	0.32	0.89	1.97	1.79	0.45	0.32	0.29
	4	0.32	0.16	1.00	2.00	1.00	0.50	0.50	0.00
	5	0.57	0.29	1.07	2.75	1.17	0.54	0.07	0.22
Resource costs									
Unit costs ($)		438.00[a]	10,966.74[b]	100.62[c]	61.55[d]	9.15	47.86[e]	46.38[f]	61.35[g]

CT = computed tomography; ER = emergency room; GP = general practitioner; hosp. = hospitalization; H&Y = Hoehn and Yahr; MRI = magnetic resonance imaging; neur = neurologist; psych = psychiatrist.

Note: Nurse cost based on a 15-minute visit.

[a] Ontario Case Costing Tool (diagnosis G20).[18]

[b] Canadian Institute for Health Information Patient Cost Estimator.[31]

[c] Ontario Schedule of Benefits Physician Services (average of A186, A183, A184, A181, A188 plus E078).[19]

[d] Ontario Schedule of Benefits Physician Services (average of A005 and A006).[19]

[e] Ontario Schedule of Benefits Physician Services (A195).[19]

[f] Ontario Schedule of Benefits Laboratory Services (X421 and E875).[20]

[g] Ontario Schedule of Benefits Laboratory Services (average of X188, X400, and X401).[20]

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

Summary of Sponsor Data Sources

Table 14: Model Data Sources

Data input	Description of data source	Comment
Baseline cohort characteristics	The baseline characteristics of the model population were based on the sponsor-conducted clinical trial Study 016:[5] mean age of 60 years, 72.0% male, 47.0% of patients in H&Y stage 2, 39.0% in stage 3, and 14.0% in stage 4. Based on the OFF categories, 31.5% were in OFF 1, 59.1% in OFF 2, 8.5% in OFF 3, and 0.9% in OFF 4.	Uncertain. The patient cohort utilized in the model may not be representative of the patient population in Canada. A recent report from Statistics Canada reported a mean age of 66.2 years at diagnosis, with between 79% and 97% of patients being over the age of 65.[32] Additionally, the clinical expert stated the proportion of males in the study was higher than what is normally seen in clinical practice (approximately 60% male). The impact of baseline

Data input	Description of data source	Comment
		characteristics was explored as part of CADTH's scenario analyses.
Dosing	Dosing for the comparator treatments was informed by the ITC [redacted]. Safinamide doses were as per product monograph (i.e., 50 mg and 100 mg).	Uncertain whether the mean dosing used is generalizable to the Canadian setting and it is unclear if optimal doses of comparators were used in the studies.
Efficacy	The change in total OFF time per day with each treatment was derived from the sponsor-submitted ITC using safinamide 50 mg and 100 mg.	[redacted]
Natural history	Disease progression (transitioning between H&Y stages) rates were obtained from Johnson et al. (2013)[7] and converted to 6-month probabilities.	Uncertain. The clinical expert consulted by CADTH highlighted that the H&Y scale is rarely used in current practice and the use of UPDRS is a more appropriate outcome measurement to assess the progression of PD patients.
Utilities	Derived from Lowin et al. (2017)[10] according to time spent in OFF and H&Y stage. Utility decrements were obtained from Sullivan et al. (2004);[14] the CADTH Movapo Review,[15] which was derived using Walter and Odin (2015);[16] clinical experts; or sponsor assumptions.	Uncertain. See limitations section. Uncertain. See limitations section.
AEs	Discontinuation probabilities due to treatment-related AEs were obtained from the sponsor-submitted ITC. Patients discontinuing treatment due to AEs would be immediately switched to an alternate adjuvant therapy. AE rates were based on RCTs in the ITC.	[redacted] Uncertain. The inclusion of only short-term RCTs by the sponsor to inform AEs may not accurately reflect the long-term safety of PD treatments, as noted in the limitations section.
Mortality	Statistics Canada life tables starting at age 60[33] multiplied by a weighted HR for death due to PD derived from Jones et al. (2012).[9]	Uncertain. Statistics Canada life tables already include patients with Parkinson disease but, given the 0.1% to 2.1% prevalence in the age 45+ population,[34] double counting is unlikely to have an impact. No other publications assessing PD-specific mortality in Canada were identified.

Data input	Description of data source	Comment
Resource use and costs		
Drug	Safinamide acquisition cost was based on the sponsor's submitted price. Other drug-acquisition costs were from the Ontario Drug Benefit[3] and Saskatchewan Drug Plan[4] formularies. The average dose for adjuvant medication was calculated using maintenance doses from the trials.	Acceptable. Acceptable, although confidential pricing agreements may be in place, reducing the cost to drug plans for some comparators. The sponsor also excluded trials that exceeded the dosing indicated by Heath Canada to calculate the average dose, which may underestimate the treatment costs of comparators.
AEs	The sponsor applied AE costs from the CADTH Movapo Review[15] for dyskinesia, nausea, somnolence, and hallucinations. Based on clinical expert opinion, the sponsor assumed all other AEs included in the economic model would receive a GP or specialist visit to manage the AE.	Sources acceptable. The resource costs for specialist visits and GPs were lower compared with the costs used in CADTH's previous review of Movapo;[15] however, results favoured the comparators and the overall impact on the economic model was minimal.
Health state	Frequencies of hospitalizations, ER visits, professional visits, and monitoring tests were obtained from Findley et al. (2011),[17] adjusted and validated by Canadian clinical experts according to H&Y and OFF health states. Linear extrapolation was applied to limited or missing data. Costs were obtained from the CIHI Patient Cost Estimator[31] for hospitalization, Ontario SoB for Physician Services[19] for professional services, Ontario SoB for Laboratory Services[20] for monitoring tests, and OCCI[18] for ER visits.	Sources acceptable. Sources acceptable. The resource costs for specialist visits and hospitalization were lower compared with the costs used in CADTH's previous review of Movapo;[15] however, results favoured the comparators and the overall impact on the economic model was minimal.

AE = adverse event; CIHI = Canadian Institute for Health Information; ER = emergency room; GP = general practitioner; H&Y = Hoehn and Yahr; HR = hazard ratio; ITC = indirect treatment comparison; OCCI = Ontario Case Costing Initiative; PD = Parkinson disease; RCT = randomized controlled trial; SoB = Schedule of Benefits; UPDRS = Unified Parkinson's Disease Rating Scale.

Summary of Key Assumptions

Table 15: Sponsor's Key Assumptions

Assumption	Comment
The sponsor focused on safinamide 100 mg as the primary intervention, since the majority of patients (90.9%) were receiving 100 mg per day in the SETTLE study.	Uncertain. Although the majority of patients may be receiving safinamide 100 mg, a small proportion of the patient population will likely be treated with safinamide 50 mg, which may impact the overall efficacy and safety associated with safinamide. The sponsor presented results for safinamide 50 mg as part of sensitivity analyses; however, combined results of safinamide 50 mg and 100 mg were not explored.
Patients with H&Y stage 1 have minimal or no motor impairment and were assumed not to receive adjuvant treatment.	Uncertain. Although only representing a small proportion of the trial, 3% (n = 18) of PD patients with H&Y stage 1 were included in Study 016,[5] indicating this subpopulation may receive treatment in practice. However, the clinical expert consulted by CADTH indicated patients would likely not receive treatment until bilateral involvement of PD (H&Y stage 2); therefore, CADTH considered this assumption to be reasonable.

Assumption	Comment
Patients were assumed to be awake for an average of 16 hours per day.	Reasonable, based on clinical expert feedback; however, the expert noted that PD patients are likely to experience a reduction in sleep as a result of their disease. The impact of hours spent awake was explored as part of the CADTH scenario analyses.
The sponsor assumed that when calculating the time spent in OFF for each health state, months with missing data for safinamide 50 mg and 100 mg would have the same time spent in OFF as the previous month with data.	Uncertain. It is unclear what the impact of using the last observation carried forward methodology may have on the treatment effect of safinamide. This may potentially overestimate or underestimate the benefit associated with safinamide.
Patients could only transition by a maximum of one H&Y stage during a 6-month cycle.	Acceptable, based on feedback from the clinical expert.
The sponsor indicated that only a small proportion of patients would progress to more advanced therapies (i.e., DBS or levodopa/carbidopa intestinal gel) and excluded these events from the analysis.	Reasonable. The clinical expert consulted by CADTH noted that advanced therapies such as DBS are expected to be utilized within the 10-year time horizon; however, the impact of safinamide on these therapies is expected to be minimal.
Time horizon and cycle length.	Reasonable, based on feedback from the clinical expert, as patients are likely to transition to more advanced therapies after 10 years. A 6-month cycle length was considered acceptable by CADTH, as published models for PD populations have used the same cycle length.[10,16,21,22,35,36] Additionally, CADTH's previous review of Movapo also suggested that a 6-month cycle length is appropriate.[15] A half-cycle correction should have been applied to costs and QALYs; however, this is likely to have had only a minor impact on results.
Treatment discontinuation would only occur due to AEs and patients would be immediately switched to an alternative adjuvant therapy based on previous treatment class used.	Inappropriate. The clinical expert highlighted that most AEs could be managed as part of routine care and not all patients would discontinue treatment due to AEs. Additionally, patients are more prone to discontinue treatment due to a lack of efficacy or other factors, including allergic reactions, which were not included as part of the sponsor's economic submission. There is uncertainty regarding the time on initial treatment, as this may be underestimated in the sponsor's economic model when using a 10-year time horizon (4.85 years for safinamide 100 mg). The time on treatment from Study 016/018 (102-week duration) indicates patients may be more likely to stay on treatment (1.87 years) than what is currently indicated in the model. It is unclear whether patients would withdraw from certain AEs and the impact that discontinuation due to lack of efficacy would have on safinamide cost-effectiveness.
Subsequent adjuvant treatments were assumed to have the same efficacy as safinamide 100 mg.	Inappropriate. Although CADTH considered the assumption of equal efficacy for subsequent treatments to be reasonable, the impact of assuming treatment efficacy is equal to safinamide is uncertain. The impact of subsequent treatment efficacy was explored as part of CADTH's scenario analyses using the efficacy of entacapone and selegiline as per the treatment algorithm presented by the sponsor. Additionally, CADTH considered removing the costs and QALYs associated with subsequent treatment to isolate the effect associated with safinamide as initial treatment.

Assumption	Comment
Acute and chronic AEs were assumed to occur for 2 months and 6 months, respectively, and a utility decrement was applied for the duration of the AE.	Uncertain. The clinical expert consulted by CADTH stated advanced PD patients (i.e., H&Y stage 4 or 5) may be more willing to tolerate some AEs (i.e., nausea, somnolence, hallucination) to remain on treatment and the impact on quality of life was expected to be manageable. The sponsor's assumption, therefore, may overestimate the impact of AEs due to treatment. Since AEs were not stratified according to H&Y stage, CADTH was unable to assess the impact of differential AE utility decrements according to disease severity.
Applied an average utility decrement of all AEs for hallucination using Sullivan et al. (2004),[14] as no data were available. Assumed patients experiencing worsening PD would have a 10% reduction in quality of life.	Uncertain. The clinical expert consulted by CADTH highlighted that patients experiencing hallucinations would receive additional medication to manage these symptoms and the impact on quality of life may be manageable. Inappropriate. The clinical expert consulted by CADTH stated the worsening of PD is likely not due to the treatment but instead a result of natural disease progression or lack of treatment efficacy. Additionally, as utility scores are incorporated in the economic model based on time spent in OFF and H&Y stage, this would account for worsening PD and result in a double counting of the reduction in quality of life.

AE = adverse event; DBS = deep brain stimulation; H&Y = Hoehn and Yahr; PD = Parkinson disease; QALY = quality-adjusted life-year.

Sponsor Scenario Results

Table 16: Results of the Sponsor's Scenario Analysis – Safinamide 50 mg

Treatment	Total costs ($)	Total QALYs	Pairwise ICUR versus safinamide ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated strategies				
Selegiline	138,176	3.403	36,483	–
Pramipexole	141,121	3.716	82,153	32,647
Bromocriptine	152,784	3.970	Dominates safinamide	158,817
Dominated strategies				
Entacapone	147,336	3.854	188,399	Extendedly dominated by bromocriptine
Rasagiline	149,790	3.815	75,798	Dominated by entacapone
Ropinirole	144,063	3.615	42,940	Dominated by pramipexole
Rotigotine	163,522	3.726	Dominated by safinamide	Dominated by bromocriptine and entacapone
Safinamide 50 mg	**156,388**	**3.902**	**–**	**Dominated by bromocriptine**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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

Over the 10-year time horizon, safinamide 50 mg is $18,000 more costly than selegiline, and $3,500 more costly than bromocriptine. Based on the sponsor's ITC results, [redacted]. Safinamide 50 mg was associated with more QALYs when compared with selegiline (+0.50) and fewer QALYs when compared with bromocriptine (−0.07); however, there is uncertainty regarding the difference in treatment effect between safinamide doses [redacted].

CADTH CDR Reanalyses

In CADTH's reanalyses, transition probabilities based on the four OFF categories (Table 17) were applied directly in the Markov traces to safinamide and all comparators for both initial and subsequent treatment beyond 24 months (treatment cycle 5+).

Table 17: Transition Probabilities According to Time Spent in OFF Categories

Transitions	Mean value
OFF 1 to OFF 2	0.126
OFF 2 to OFF 3	0.077
OFF 3 to OFF 4	0.047

Source: Kalabina et al. (2019)[21] and Lowin et al. (2017).[10]

Base-Case Results

Table 18: Results From CADTH Reanalyses – Safinamide 100 mg

	Description	Treatment	Sequential ICUR ($/QALY)
	Submitted sponsor base case	Selegiline	–
		Entacapone	80,054
		Bromocriptine	107,521
		Safinamide 100 mg	Dominated by bromocriptine
1	Corrected sponsor base case[a]	Selegiline	–
		Entacapone	81,017
		Bromocriptine	109,390
		Safinamide 100 mg	Dominated by bromocriptine
2	Kalabina et al. utilities	Selegiline	–
		Bromocriptine	86,880
		Safinamide 100 mg	Dominated by bromocriptine
3	Removal of worsening PD decrement	Selegiline	–
		Bromocriptine	149,900
		Safinamide 100 mg	Dominated by bromocriptine and entacapone
4	Long-term OFF transition probabilities	Selegiline	–
		Entacapone	61,349
		Bromocriptine	123,886
		Safinamide 100 mg	Dominated by bromocriptine
5	**CADTH base case (1 + 2 + 3 + 4)**	**Selegiline**	**–**
		Bromocriptine	**123,612**
		Safinamide 100 mg	**Dominated by bromocriptine**

ICUR = incremental cost-utility ratio; PD = Parkinson disease; QALY = quality-adjusted life-year.

Note: Only non-dominated strategies and safinamide results presented.

[a] CADTH correction of calculation errors in the model. Corrections included incorporation of PD mortality hazard ratio probabilistically.

Table 19: Cost Breakdown for CADTH Base Case

	Drug costs ($)	Direct medical costs ($)	Direct non-medical costs ($)	AE costs ($)	Total costs ($)	Time on initial treatment (years)
Bromocriptine	17,100	51,978	98,034	262	167,373	2.93
Entacapone	12,300	52,045	96,656	350	161,350	4.26
Pramipexole	11,560	50,752	93,883	619	156,815	5.12
Rasagiline	16,470	51,686	95,512	382	164,050	5.00
Ropinirole	12,192	51,194	94,323	770	158,480	5.67
Rotigotine	31,682	50,824	93,645	533	176,684	5.80
Safinamide 100 mg	21,343	51,580	95,443	358	168,725	4.85
Selegiline	12,056	49,895	91,354	517	153,823	7.71

AE = adverse event.

Source: Calculated from sponsor's model.

Scenario Results

Table 20: Results from CADTH Reanalyses – Safinamide 50 mg

Description	Treatment	Total costs ($)	Total QALYs	Pairwise ICUR versus safinamide ($/QALY)	Sequential ICUR ($/QALY)
CADTH base case (1 + 2 + 3 + 4)	**Non-dominated strategies**				
	Selegiline	154,424	3.539	164,949	–
	Entacapone	161,309	3.670	Dominates safinamide	52,816
	Bromocriptine	167,217	3.741	Dominates safinamide	83,205
	Dominated strategies				
	Pramipexole	156,431	3.479	89,166	Dominated by selegiline
	Rasagiline	164,197	3.671	Dominates safinamide	Extendedly dominated by bromocriptine
	Ropinirole	158,634	3.386	47,654	Dominated by selegiline
	Rotigotine	178,653	3.569	Dominated by safinamide	Dominated by bromocriptine, entacapone, rasagiline
	Safinamide 50 mg	**170,599**	**3.638**	**–**	**Dominated by bromocriptine, entacapone, rasagiline**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 21: Results from CADTH Scenario Analyses – Safinamide 100 mg

	Scenario	Treatment	Total cost ($)	Total QALYs	Sequential ICUR ($/QALY)
5a	Patient age – 65	Selegiline	147,504	3.566	–
		Bromocriptine	160,695	3.669	128,603
		Safinamide 100 mg	161,976	3.534	Dominated by bromocriptine
5a	Percent male – 60%	Selegiline	154,284	3.689	–
		Bromocriptine	167,878	3.798	123,845
		Safinamide 100 mg	159,181	3.742	Dominated by bromocriptine and entacapone
5b	Time spent awake – 14 hours	Selegiline	155,369	3.648	–
		Bromocriptine	168,654	3.758	120,547
		Safinamide 100 mg	170,787	3.692	Dominated by bromocriptine
5b	Time spent awake – 18 hours	Selegiline	152,481	3.697	–
		Entacapone	159,530	3.759	114,013
		Bromocriptine	166,230	3.807	138,976
		Safinamide 100 mg	166,972	3.757	Dominated by bromocriptine and entacapone
5c	AEs applied to first cycle only	Selegiline	153,152	4.062	–
		Safinamide 100 mg	168,217	3.983	Dominated by pramipexole and selegiline
5d	Utilities from Lowin et al.	Selegiline	153,708	3.834	–
		Entacapone	161,213	3.900	114,328
		Bromocriptine	167,258	3.938	157,625
		Safinamide 100 mg	168,598	3.898	Dominated by bromocriptine and entacapone
5e	Subsequent treatment efficacy – entacapone	Selegiline	153,837	3.674	–
		Bromocriptine	167,793	3.775	137,552
		Safinamide 100 mg	168,974	3.722	Dominated by bromocriptine
5e	Subsequent treatment efficacy – selegiline	Selegiline	153,238	3.687	–
		Bromocriptine	165,642	3.820	93,499
		Safinamide 100 mg	167,472	3.753	Dominated by bromocriptine and entacapone
5f	Removal of subsequent treatment costs and utilities	Bromocriptine	44,890	1.068	–
		Entacapone	63,043	1.448	40,453
		Selegiline	116,028	2.850	41,034
		Safinamide 100 mg	80,995	1.803	Dominated by rasagiline

AE = adverse event; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: Only non-dominated strategies and safinamide results presented.

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