CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

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's 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.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that safinamide should not be reimbursed for the treatment of 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.

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SAFINAMIDE (ONSTRYV — VALEO PHARMA INC.)

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that safinamide should not be reimbursed as 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.

Reasons for the Recommendation

1. In two 24-week, multicenter, double blind (DB), placebo-controlled Phase III randomized controlled trials (RCTs) conducted in adult patients with idiopathic PD, safinamide did not show a clinically meaningful improvement over placebo in change from baseline to Week 24 in ON time, the primary outcome in each trial. In SETTLE (N=549), the difference in change from baseline between safinamide 50 mg/day to 100 mg/day and placebo was 0.96 hours in daily ON time (95% CI, 0.56 to 1.37; P < 0.001) in favour of safinamide. In Study 016 (N=669), the difference in change from baseline between safinamide 50 mg/day compared with placebo was 0.51 hours (95% CI, 0.07 to 0.94; P = 0.0223) and the difference in change from baseline between safinamide 100 mg/day and placebo was 0.55 hours (95% CI, 0.12 to 0.99; P = 0.0130); both differences were in favour of safinamide. CDEC did not consider these changes to be clinically significant for either dose of safinamide, based on a minimum clinically important difference of 1 to 2 hours.
2. For the assessment of daily OFF time at Week 24 in SETTLE, the difference in change from baseline between safinamide 50 mg/day to 100 mg/day and placebo was –1.03 hours (95% CI, –1.40 to –0.67; P < 0.001) in favour of safinamide. In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was –0.6 hours (95% CI, –0.9 to –0.2; P = 0.0043) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was –0.6 hours (95% CI, –1.0 to –0.2; P = 0.0034) in favour of safinamide. The difference in SETTLE met the published minimally important difference (MID) in OFF time (-1 to -1.3 hours), however, the upper bound of the 95% confidence interval is outside the MID range. These differences did not meet the MID thresholds in Study 016. Some patients might find these reductions in OFF time of clinical relevance, however, CDEC could not determine which patients may respond given the trial data and the fact that the comparator is placebo, not another MAO-B inhibitor or another add-on agent already used currently in the management of PD.
3. The relative efficacy of safinamide compared with other add-on treatments used for PD is unclear due to major limitations associated with the manufacturer-submitted indirect treatment comparison (ITC) and one published ITC by Binde et al., 2018. The main limitations of both studies were inadequate reporting of study and patient characteristics. The manufacturer-submitted ITC was also limited by uncertainty around clinical heterogeneity of the included studies, and an absence of information on dosages of comparators. These limitations preclude definitive conclusions from being drawn regarding the efficacy and safety of safinamide compared with other treatments for PD. The lack of comparative data to other MAO-B inhibitors, in particular, makes the reversible inhibition mechanism of safinamide uncertain in terms of clinical impact on the patient.
4. There is no evidence that safinamide addresses an unmet need that is not already addressed by other add-on treatments currently reimbursed for the treatment of PD, including better management of OFF episodes, improved quality of life, or improved non-motor outcomes relevant to patients such as sleep, pain, mood and constipation. The EQ-5D and Patient's Global Impression of Change were only assessed in SETTLE and not included in the statistical testing hierarchy. In both trials, symptom-related outcomes pertaining to depression and mental state (grid version of Hamilton Rating Scale for Depression [GRID-HAM] and Mini-Mental State Examination [MMSE]) were not included in the statistical testing hierarchies. Study 016 did not include the PDQ-39, and SETTLE did not include the Dyskinesia Rating Scale in their statistical testing hierarchies; these outcomes were not adjusted for multiplicity and are at risk of an inflated type I error.

Discussion Points

- CDEC noted that safinamide is a reversible inhibitor of monoamine oxidase B (MAO-B), which is unlike other available MAO-B inhibitors (rasagiline and selegiline) that are irreversible inhibitors. Reversible MAO-B inhibition may improve tolerability over irreversible MAO-B inhibitors, however evidence of this benefit is still required.
- CDEC noted that adverse events (AEs) of dyskinesia and nausea occurred more frequently in the safinamide arms compared with placebo. Although the anti-glutamate effects of safinamide may cause less dyskinesia than other MAO-B inhibitors, there are no comparative trials with other MAO-B inhibitors to directly estimate the relative effects on dyskinesia.
- CDEC noted that the submitted cost-effectiveness analysis found that both safinamide 50 mg and 100 mg were dominated (i.e., associated with greater costs and fewer quality-adjusted life years [QALYs]) by other treatments for PD. However, several limitations with the submitted analysis were identified that could not be addressed, including major limitations with the methods for the indirect treatment comparison (ITC) that prevent conclusions being drawn regarding the efficacy and safety of safinamide compared to other treatments already available. As such the cost-effectiveness of safinamide remains uncertain.
- CDEC noted that both SETTLE and Study 016 had inclusion and exclusion criteria for patient eligibility that excluded patients with late stage PD (i.e. only included patients with a Hoehn and Yahr stage of 1-4 during an OFF phase). Only 14% of patients had stage 4 PD and no patients had stage 5 disease. No patients were included that were experiencing severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations in their symptoms, as well with certain comorbidities (e.g., depression). The exclusion criteria in SETTLE and study 016 therefore created a selective study population and limit generalizability to the Canadian PD population.
- CDEC noted that a published ITC also reviewed by CADTH suggested improved efficacy of safinamide compared to placebo in the Unified Parkinson's Disease Rating (UPDRS). However, the quality and therefore utility of the published ITC was limited due to poor reporting of methods and patient characteristics.
- CDEC noted that insufficient evidence was available to address other issues of concern to patients, in particular the need for medications with quick onset, the benefits of reduced pill burden on compliance, and improvements in overall quality of life.

Background

Safinamide has a Health Canada indication as an 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. Safinamide is a highly selective and reversible inhibitor of monoamine oxidase B. It is available as 50 mg and 100 mg tablets (as safinamide mesylate) for oral use. According to the Health Canada–approved dose, treatment with safinamide should be started with a dose of 50 mg once per day, administered orally. After two weeks the dose may be increased to 100 mg once per day based on individual clinical need and tolerability.

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the Common Drug Review: a systematic review of randomized control trials (RCTs) of safinamide and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with PD and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups (Parkinson Canada and Parkinson Society British Columbia) provided input for this submission. Patient perspectives were obtained from surveys and interviews. The following is a summary of key input from the perspective of the patient groups:

- The patient groups' input indicated that "loss of confidence" (often related to due to medication "wearing off" or "OFF times") experienced since developing PD had a great impact that on daily life. Many patients indicated the negative impact on their ability to socialize and maintain relationships because they have had to stop engaging in recreational activities (e.g., sports) or family life. Patients with PD 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, slowness of movement. Caregivers most

often reported a lack of time due to the demands of caring for a person with PD and the associated challenges of maintaining social and/or recreational activities.

- Patients surveyed indicated experience with a range of different symptomatic treatments including medications (e.g., MAO inhibitors and levodopa carbidopa), surgical procedures (e.g., Deep Brain Stimulation), other forms of therapy (e.g., physiotherapy, occupational therapy, speech therapy, exercise) and psychological follow up. Common side effects when taking medications including disturbed sleep, nausea, constipation, dyskinesia, fatigue and hallucinations. Some patients also reported difficulties in receiving treatment including swallowing, remembering to take medication, and timing their medication with meals. Patients who used levodopa reported dyskinesia or involuntary writhing movements, and people in an advanced state of PD frequently experience these when they are 'ON' to a severe extent. However, without levodopa, they are then reduced to an "OFF" state, an even more disabling, frightening stage where breathing and swallowing are at risk.
- Patients reported the need for a medication that would cure, stop disease progression and effectively control symptoms. There is also an expressed need for medications with quicker onset, a lower pill burden, that last longer and limit or eliminate "OFF" times, and with less side effects such as hallucinations.

Clinical Trials

The systematic review identified SETTLE (N = 549) and Study 016 (N = 669). These trials were 24-week, multicenter, double blind, placebo-controlled RCTs conducted in adult patients with idiopathic PD. The objective of SETTLE was to evaluate the safety and efficacy of a dose range of safinamide 50 mg to 100 mg, compared with placebo as add-on therapy in patients with idiopathic Parkinson's disease with motor fluctuations, who are receiving a stable dose of levodopa. In SETTLE, patients were randomized in a 1:1 ratio to treatment with safinamide 50 mg/day to 100 mg/day or placebo.

The objective of Study 016 was to evaluate the efficacy and safety of two oral doses of safinamide (50 mg/day and 100 mg/day) compared with placebo, as add-on therapy in patients with idiopathic PD with motor fluctuations, who were currently receiving a stable dose of levodopa. In Study 016, patients were randomized in a 1:1:1 ratio to treatment with safinamide 50 mg, safinamide 100 mg/day, or placebo. In both trials the primary efficacy outcome was change from baseline to Week 24 in daily ON time.

Key limitations of SETTLE and Study 016 related to the eligibility criteria that reduced the generalizability of the trials to the Canadian clinical population and the lack of evidence comparing safinamide to other active treatments. Both SETTLE and Study 016 had inclusion and exclusion criteria for patient eligibility that excluded patients with late stage of PD or certain comorbidities (e.g., depression). The exclusion criteria created an enriched study population and may represent a population who may be more likely to respond to the treatment. Study 016 included a study population composed of 80% Asian patients (recruited from India) which may have an impact on generalizability to the Canadian population. The doses of safinamide in Study 016 (50 mg/day, 100 mg/day) were associated with separate trial arms and were not representative of dose administration in clinical practice, where patients would start on the 50 mg/day dose and increase the dose to 100 mg/day depending on tolerability.

In SETTLE and Study 016 the proportion of patients that discontinued the trial was similar between trial arms with the most common reason for discontinuation attributed to adverse events. In SETTLE, 10.6% of patients in the safinamide 50 mg/day to 100 mg/day arm discontinued compared with 12.4% in the placebo arm. In Study 016, 9.4% patients in the safinamide 50 mg/day arm, 12.9% of patients in the safinamide 100 mg/day, and 11.3% of patients in the placebo arm discontinued the trial. Dyskinesia occurred more frequently in the safinamide arms in both trials compared with placebo; this difference creates the potential for unblinding for patients and investigators.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: motor examination score (UPDRS Section III), daily ON time, daily OFF time, dyskinesia rating scale, activities of daily living scale (UPDRS Section II), EuroQol 5D. The primary outcome in both trials was change from baseline to Week 24 in daily ON time.

- Motor Examination Score (UPDRS Section III): The UPDRS Section III assesses motor examination. This section of the UPDRS consists of 14 items, with 27 separate ratings on a scale from 0 (normal/absent/ none) to 4 (severe impairment), with a total range in score of 0 to 108 where higher scores indicate worse symptoms. The Minimal important difference (MID) for the UPDRS Section III has been identified in the literature at 2.0 units to 6.2 units in patients with early PD (Hoehn and Yahr Stage

of I to 3), and 5.2 units for varying stages of PD. The clinical expert consulted for this review stated that a clinically relevant difference would be 4.0 units.

- ON/OFF time: ON and OFF time were assessed using diary cards maintained by patients over a period of 18 hours (6 AM to midnight) each day for three consecutive days at 30-minute intervals. At each interval the patient or caregiver recorded if the patient was: in an ON phase without dyskinesia; in an ON phase with non-troublesome/minor dyskinesia; in an ON phase with troublesome dyskinesia; in an OFF phase; asleep. The ON phase was defined as the patient functioning as well as can be expected for that patient, irrespective of whether or not he or she was having dyskinesias. OFF time was defined as a lack of mobility, bradykinesia, or akinesia and assessed using diary cards. The validity and reliability of the diary cards used to assess ON time has been assessed in the literature. MID values for ON time were not identified in the literature, however input from the clinical expert consulted for this review stated that the minimal clinically relevant difference would be 1 hour to 2 hours. Similar to ON time, the validity and reliability of diary card used to assess OFF time has been assessed in the literature. The MID for improvement in OFF time has been identified at –1 hour to –1.3 hours.
- Dyskinesia rating scale: The dyskinesia rating scale includes a set of 3 tasks to measure severity of dyskinesia in PD with each item scored on a 5-point ordinal scale from 0 to 4. Higher scores correspond with more severe dyskinesia. No evidence of validity and limited evidence of reliability were identified in the literature. A MID has not been identified in the literature.
- Parkinson's Disease Questionnaire 39 (PDQ-39): The PDQ-39 is a disease specific HRQoL measure consisting of eight domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort); graded on a five-point scale (0 = never; 4 = always). Each domain is coded on a scale of 0 (no problem at all) to 100 (maximum level of a problem). Further, an overall single summary index (PD summary index, PDQSI) representing the global HRQoL can be created by averaging the eight subscale scores. The PDQSI is also coded on a scale ranging from 0 to 100, with higher scores indicating worse quality of life. The validity and reliability of the PDQ-39 has been assessed in the literature. The MID for the overall PDQ-39 score has been identified at –1.6 units.
- Grid-based 17-item Hamilton Rating Scale for Depression (GRID-HAMD-17): The GRID-HAMD is based on the 17-item Hamilton Rating Scale for Depression, which is a widely used measure in clinical trials for major depressive disorder. Each of the 17 items, which assess symptoms, is rated both in frequency and severity. Item scores range from 0 to 4 or 0 to 2, with higher scores corresponding to greater frequency and/or intensity. The possible score range is 0 to 52. Limited validity and acceptable reliability of the GRID-HAMD-17 has been identified in the literature. A MID for patients with PD has not been identified in the literature.
- Mini-Mental State Examination (MMSE): The MMSE is a brief, commonly-used test to assess cognitive function. It consists of 11 items that evaluate attention and orientation, memory, registration, recall, calculation, language, and ability to draw a complex polygon. The score ranges from 0 to 30, with lower scores corresponding with increasing cognitive impairment. The validity and reliability of the MMSE has been assessed in the literature. A MID for patients with PD has not been identified in the literature.
- EuroQol 5-Dimensions 3-Levels: The EQ-5D-3L is a generic, preference-based, HRQoL measure consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels representing no problems (1), some problems (2), and extreme problems (3). The validity of the EQ-5D-3L has been assessed in the literature. A MID for the index score in patients with PD has been identified at 0.10 to 0.11 units.
- Patient's Global Impression of Change (PGIC): The PGIC assess the change in the patient's overall clinical status from baseline to various time points during the study using a seven-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.
- Activities of daily living scale (UPDRS Section II): The UPDRS Section II assesses Activities of Daily Living (ADL). This section of the UPDRS consists of 13 activities of daily living with each item rated on a scale of 0 (normal) to 4 (severe impairment), with a total range in score of 0 to 52 where higher scores indicating greater impairment. The validity and reliability of the ADL has been assessed in the literature. The MID for the ADL score has been identified at 0.5 units to 2.2 units in patients with early PD (Hoehn and Yahr Stage of 1 to 3).
- Harms were assessed as the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), deaths, and notable harms (e.g., dyskinesia).
- Data were not available for frequency of patient-rated ON or OFF episodes, an outcome indicated to be important to patients.

Efficacy

Based on the primary outcome (change from baseline to Week 24 in daily ON time assessed via diary), treatment with safinamide (50 mg/day to 100 mg/day in SETTLE; 50 mg/day, and 100 mg/day in Study 016) showed statistically (but not clinically) significant improvement compared with placebo in both trials at Week 24 based on a MID of 1 hour to 2 hours. Similar findings were reported in Study 016 for the assessment of OFF time, and a statistically significant and clinically relevant improvement was observed for safinamide 50 mg/day to 100 mg/day in SETTLE when compared with placebo based on a MID of –1 hour to –1.3 hours. Subgroup analysis for patients only treated with levodopa and their assigned treatment generally reflected the results of the main analysis, although greater numerical differences were observed between treatment arms. Overall, these findings confirm a statistically significant impact of safinamide on PD-related motor fluctuations. Although superior to placebo, the differences captured by the diaries indicate only a modest clinical impact.

According to the clinical expert consulted in this review, along with the improvement of motor fluctuations, a positive effect on mobility (as assessed by the Motor Examination Score [UPDRS Section III]) and activities of daily living (assessed by the ADL score [UPDRS Section II]) is useful for determining a clinically meaningful response to treatment in patients with PD; this was echoed by the patient groups who provided input for this review. In both trials, the change from baseline in Motor Examination Score showed statistically significant improvements for treatment with safinamide (50 mg/day to 100 mg/day in SETTLE; 50 mg/day, and 100 mg/day in Study 016) compared with placebo in both trials at Week 24; clinically relevant improvements were only found for safinamide 100 mg/day in Study 016 based a MID of 2.0 units to 6.2 units. Motor Examination Score assessment was adjusted for multiplicity in both trials. For the change from baseline in ADL score, the safinamide 100 mg/day arm in Study 016 was the only treatment that showed both a statically significant and clinically relevant improvement compared with placebo based on a MID of 0.5 units to 2.2 units. ADL assessment was adjusted for multiplicity in both trials.

The clinical expert consulted for this review stated that reduction of dyskinesia was among the outcomes that are considered in determining a clinically meaningfully response to treatment, however based on the DRS, treatment with safinamide was no different than placebo for any of the doses considered in the trials. The DRS assessment was adjusted for multiplicity in Study 016 but not in SETTLE.

Improvement with respect to the PDQ-39 showed statistically and clinically meaningful differences in SETTLE for safinamide 50 mg/day to 100 mg/day. The PDQ-39 assessment was adjusted for multiplicity in SETTLE but not in Study 016. Symptom-related outcomes pertaining to depression and mental state assessed using the GRID-HAM and MMSE, respectively, showed no difference compared with placebo for any of the doses considered in the trials. Neither outcome was adjusted for multiplicity in the trials. HRQoL outcomes using the EQ-5D-3L and patient satisfaction using the PGIC were assessed in SETTLE only and showed statistically significant differences for safinamide 50 mg/day to 100 mg/day compared with placebo, although neither outcome was adjusted for multiplicity.

While the outcomes assessed in the trials were relevant to the clinical population with PD, outcomes related to the frequency of patient-rated ON or OFF episodes, time to response, and use of healthcare services were not assessed in either trial. Important outcomes (EQ-5D and PGIC) were only assessed in SETTLE and were not included in the statistical testing hierarchy. In both trials, symptom-related outcomes pertaining to depression and mental state (GRID-HAM and MMSE) were not included in the statistical testing hierarchy in either trial. Study 016 did not include the PDQ-39, and SETTLE did not include the DRS in each of their statistical testing hierarchies. These outcomes were considered territory or exploratory; they were not adjusted for multiplicity and are at risk of an inflated type I error.

The long-term extension study (Study 018) presented data for patients following their participation in Study 016 up to Week 78. Generally, the efficacy results reflected the results from Study 016 for outcomes related to ON time and UPDRS Section III and II; although some numerical reductions in efficacy were observed for treatment with safinamide 50 mg/day for motor examination (UPDRS Section III) and ADL (UPDRS Section II) compared to the results from Study 016. Efficacy outcomes should be considered exploratory as Study 018 was not powered to detect statistical differences for any of the outcomes assessed

Harms (Safety)

In SETTLE, more patients in the placebo arm (9.5%) experienced SAEs, compared with the safinamide 50 mg/day to 100 mg/day arm (6.6%). In Study 016, 3.6% of patients in the safinamide 50 mg/day and 9.8% of patients in the safinamide 100 mg/day compared with 8.1%% of patients in the placebo arm experienced SAEs.

Overall adverse events occurred similarly in patients in the safinamide arm(s) compared with placebo in both trials.

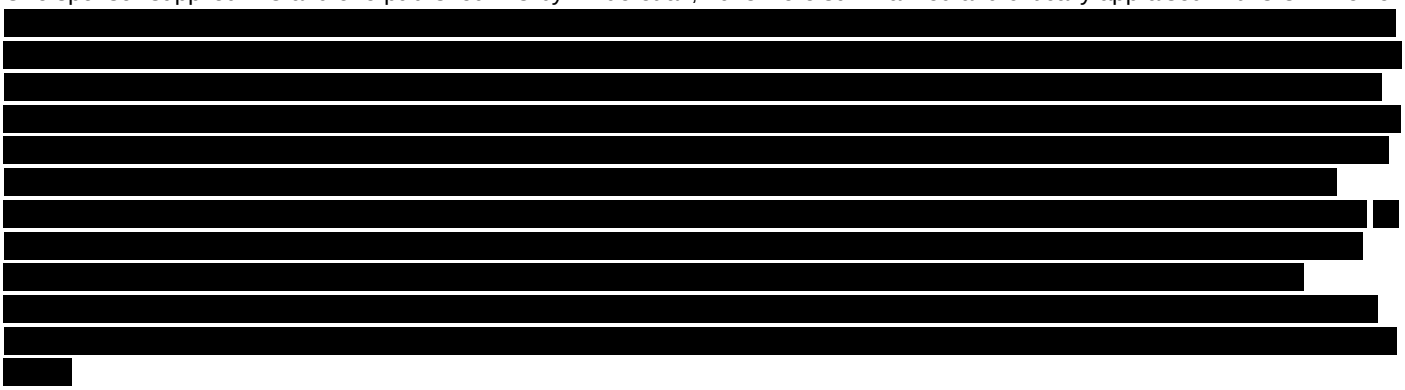
In both studies the following notable harms were reported more often in the safinamide arm(s) compared with placebo: dyskinesia, insomnia (100 mg/day dose only in Study 016), and nausea. Postural/orthostatic hypotension was reported more frequently in the safinamide arm compared with placebo in SETTLE only. Constipation, hallucinations, impulsive behavior, melanoma, and vomiting occurred similarly between the treatment arms.

The exclusion criteria in SETTLE and Study 016 created an enriched study population and may represent a population who were not at an increased risk of potential treatment-related AEs, including comorbidities, which rendered the benefit harm profile to be more optimal than what could be seen in the real-world clinical practice.

In the long-term extension study (Study 018), no new safety signals arose over the course of 78 weeks. Safety results should also be interpreted with caution given the enriched study population and limited generalizability to the Canadian population.

Indirect Treatment Comparisons

One sponsor-supplied ITC and one published ITC by Binde et al., 2018 were summarized and critically appraised in this CDR review.



The published ITC by Binde et al., 2018 summarized the indirect evidence comparing placebo plus levodopa to MAO-Bs including safinamide plus levodopa. The outcomes evaluated in this analysis include the UPDRS and SAEs. Evidence from the Binde et al., 2018 ITC suggests improved efficacy in UPDRS compared with placebo. No difference compared with placebo in the occurrence of SAEs was determined based on 95% credible intervals. The utility and quality of the Binde et al., 2018 ITC is limited due to poor reporting of methods. Limitations of this ITC include inadequate reporting of study and patient characteristics which prevent the ability to assess generalizability to the Canadian clinical population. Definitive conclusions regarding the efficacy and safety of safinamide compared to placebo can not be made based on the Binde et al., 2018 ITC.

Cost and Cost-Effectiveness

Safinamide mesylate is available as 50 mg and 100 mg tablets at a submitted price of $6.90 per tablet, regardless of strength. 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. At the recommended dose, the annual cost of treatment with safinamide is $2,520.

The sponsor submitted a cost-utility analysis comparing safinamide 100 mg to MAO-B inhibitors (rasagiline, selegiline), catechol-o-methyltransferase (COMT) inhibitors (entacapone), and dopamine agonists (bromocriptine, pramipexole, ropinirole, and rotigotine) as adjunct therapies to levodopa. The sponsor's base case was conducted from the perspective of a Canadian publicly funded

healthcare payer over a 10-year time horizon. 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 stages (H&Y; stages 2-5) and the remaining two health states were discontinuation due to AE followed by a treatment switch, and death. Patients could experience one of six scenarios every 6-months: 1) transition to more time spent in "OFF" but not progress on the H&Y scale, 2) progress on the H&Y scale but maintain time spent in "OFF", 3) progress on both the H&Y scale and time spent in "OFF", 4) maintain the current health state, 5) discontinue treatment due to AE from any health state and switch treatment, or 6) enter death from any health state. Treatment effects and probabilities of AEs were based on a sponsor-commissioned unpublished ITC. In the sponsor's base case, safinamide 100 mg was dominated by bromocriptine, i.e., safinamide was associated with greater costs and fewer QALYs as the acquisition cost of safinamide was higher, duration of treatment was longer and, according to the modelled ITC data, less time was spent in "OFF" state compared with other adjunct treatments for PD.

CADTH identified the following key limitations of the sponsor's submitted economic analysis:

- 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.
- Application of utility values and AE decrements were uncertain, specifically when including an arbitrary utility decrement for worsening PD which likely overestimated the impact of this event.
- The CADTH Clinical Review identified limitations with the ITC resulting in uncertainty of comparative effectiveness of safinamide.

The CADTH base case reflected changes to the following parameters: correction of inputs probabilistically; applying updated utilities from Kalabina et al.; removal of the worsening PD utility decrement; and, applying long-term "OFF" transition probabilities. CADTH was unable to test the impact of the lack of long-term effectiveness evidence of safinamide or discontinuation due to a lack of efficacy, nor test alternate assumptions regarding the mean time spent in "OFF" for safinamide.

In line with the sponsor's submitted base case, CADTH found that both safinamide 50 mg and 100 mg were dominated (i.e., associated with greater costs and fewer QALYs) by other treatments for PD. 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. Further, the CDR Clinical Review identified major limitations with the methods for the ITC that prevent definitive conclusions being drawn regarding the comparative efficacy and safety of safinamide. As such the true cost-effectiveness of safinamide is uncertain.

CDEC Members

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

October 16, 2019 Meeting

Regrets

2 CDEC members did not attend.

Conflicts of Interest

None

March 18, 2020 Meeting

Regrets

None

Conflicts of Interest

None