CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**SIPONIMOD (MAYZENT — Novartis Pharmaceuticals Canada Inc.)**
Indication: Secondary progressive multiple sclerosis.

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that siponimod be reimbursed for the treatment of patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability, only if the following conditions are met.

**Conditions for Reimbursement**
**Initiation Criteria**
1. Patients who have all of the following characteristics:
   1.1. a history of relapsing-remitting multiple sclerosis (RRMS) and current active SPMS
   1.2. an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5
   1.3. documented EDSS progression during the two years prior to initiating treatment with siponimod (≥ 1 point if EDSS < 6.0; ≥ 0.5 points if EDSS ≥ 6.0 at screening).
2. Siponimod should not be used in combination with other disease-modifying treatments used to treat multiple sclerosis.

**Renewal Criteria**
1. Patients should be assessed for a response to siponimod every six months.
2. Siponimod may be renewed for patients who do not exhibit evidence of disease progression since the previous assessment. Disease progression is defined as an increase in the EDSS score of ≥ 1 point if the EDSS score was 3.0 to 5.0 at siponimod initiation, or an increase of ≥ 0.5 points if the EDSS score was 5.5 to 6.5 at siponimod initiation.

**Discontinuation Criteria**
1. Treatment with siponimod should be discontinued in patients who exhibit either of the following:
   1.1. progression to an EDSS score of equal to or greater than 7.0 at any time during siponimod treatment
   1.2. confirmed worsening of at least 20% on the timed 25-foot walk since initiating siponimod treatment.

**Prescribing Conditions**
1. The patient is under the care of a specialist with experience in the diagnosis and management of multiple sclerosis.

**Pricing Conditions**
1. Reduction in price.

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2. Siponimod should not be used in combination with other disease-modifying treatments (DMTs) used to treat multiple sclerosis.

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1. Treatment with siponimod should be discontinued in patients who exhibit either of the following:
   1.1. progression to an EDSS score of equal to or greater than 7.0 at any time during siponimod treatment
   1.2. confirmed worsening of at least 20% on the timed 25-foot walk (T25W) since initiating siponimod treatment.

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1. The patient is under the care of a specialist with experience in the diagnosis and management of multiple sclerosis.

**Pricing Conditions**

1. Reduction in price.

## Reasons for the Recommendation

1. In one double-blind, phase III, randomized controlled trial (EXPAND), patients with and without active SPMS who were treated with siponimod 2 mg daily demonstrated a clinically meaningful benefit compared with placebo in reducing the time to three-month confirmed disability progression (CDP) at month 12 based on the change in EDSS score (hazard ratio [HR] = 0.79, 95% confidence interval [CI], 0.65 to 0.95; P = 0.0134). Further, results of the study suggest that siponimod may provide benefit in preventing relapses and improving imaging outcomes. The observed benefits in the subgroup of patients with active SPMS were generally consistent with the overall study population (with and without active SPMS); however, the magnitude of the treatment effect of siponimod was more evident in the active SPMS subgroups.
2. There is no evidence to support a potential benefit of siponimod in combination with immunomodulatory therapies or DMTs for multiple sclerosis. Concomitant administration of such treatments was not permitted in patients enrolled in the EXPAND study.
3. Siponimod is not a cost-effective option at a cost-effectiveness threshold of $50,000 per quality-adjusted life-year (QALY) compared with best supportive care (BSC). CADTH estimated that the incremental cost-effectiveness ratio (ICER) for siponimod compared with BSC was $194,007 per QALY. A price reduction of at least 63% would be required to achieve an ICER below a willingness-to-pay threshold of $50,000 per QALY.

## Implementation Considerations

- Siponimod is contraindicated in patients with some cytochrome P450 enzyme 2C9 genotype (CYP2C9) variants while other variants require dosage adjustments. Through its Patient Support Program, the sponsor will be responsible for the cost of CYP2C9 genotyping prior to initiating treatment with siponimod.

## Discussion Points

- Clinical experts and patients identified the need for treatment options for SPMS. Siponimod is the first treatment that has been shown to reduce disease progression in patients with active inflammatory disease; however, it is unlikely to meet the therapeutic gap for all patients with SPMS.
- Overall, the EXPAND trial was well-conducted and powered to determine a difference in the primary outcome (time to three-month CDP) for the overall SPMS population. Analyses by specific active disease groups (relapses, imaging) were planned but were outside the testing hierarchy. According to the sponsor, a post-hoc subgroup analysis in patients with active SPMS was conducted to answer questions from health authorities, but it is unlikely that randomization was maintained in this analysis.
- The EXPAND trial enrolled a highly selective patient population that did not include patients with various comorbidities (e.g., chronic immune disease, diabetes, macular edema, AIDS, HIV, hepatitis, conditions that may affect cardiovascular function, pulmonary conditions, hepatic conditions, and immune function). CDEC acknowledged that the adverse effects associated with siponimod may be higher in patients with comorbid conditions and that siponimod is contraindicated for patients with many of these conditions. In addition, treatment with siponimod in patients taking CYP2C9 and CYP3A4 inducers and inhibitors may not be appropriate in all patients; therefore, potential drug interactions must be taken into consideration when prescribing siponimod. Additional information is contained within the siponimod product monograph.
- CDEC acknowledged that siponimod may continue to offer benefit in some patients with EDSS scores over 6.5; however, there is no evidence demonstrating the potential benefit of siponimod in patients with an EDSS score of 7 or greater.
- CDEC noted that the lack of comparative data creates uncertainty with regard to its assessment of potential benefit over other treatments that may be used for patients with active SPMS. An indirect treatment comparison was submitted by the sponsor, but the analyses were not specific to patients with active SPMS; thus, the utility of the results is limited.
- For some patients, siponimod will replace their current DMT as they transition to SPMS. In these cases, there will likely be additional costs associated with an increased frequency of patient monitoring (for example, increased physician visits and MRIs). CDEC noted these additional costs were not captured in the health economic analysis.
- There will be significant drug acquisition costs associated with siponimod if prescribed to individuals with active SPMS. The economic analysis showed there was likely a health gain associated with siponimod; however, the magnitude of this benefit is uncertain. The main source of this uncertainty is derived from various inputs used in the model that are specific to a general SPMS population rather than individuals with active disease. This level of uncertainty could not be characterized by CADTH as this data were not presented.

## Background

Siponimod has a Health Canada indication for the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability. Siponimod is a sphingosine 1-phosphate receptor modulator and is available as a 0.25 mg or a 2 mg film-coated tablet. The dosage regimen recommended by Health Canada includes a six-day titration period starting with 0.25 mg and progressing up to 1.25 mg on day 5 followed by a 2 mg maintenance dose starting on day 6. The recommended maintenance dose of siponimod is 2 mg taken once daily with or without food.

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of randomized controlled trials of siponimod, a match-adjusted indirect comparison (MAIC) submitted by the sponsor, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from two clinical experts with experience treating patients with multiple sclerosis, and patient group–submitted information about outcomes and issues important to patients.

## Summary of Patient Input

One patient group, the Multiple Sclerosis Society of Canada (MS Society) provided input for this submission. Patient perspectives were obtained from an online survey. Of note, the number of patients with active versus non-active SPMS that contributed to the information used to inform the patient input submission is unknown. The following is a summary of key input from the perspective of the patient group:

- The respondents described how a diagnosis of SPMS influenced their lives: loss of independence was reported by 81% of respondents, inability to participate in physical activity by 76%, changes with the roles and responsibilities within their family by 68%, and inability to maintain employment by 56%. They expressed fear of the unknown impact that SPMS could bring to their lives and for the limited therapies available.
- For patients transitioning from RRMS to SPMS, treatment with current DMTs have little to no therapeutic benefit. Alternatively, they often no longer meet the reimbursement criteria for their current DMTs. Without an effective treatment after transitioning to SPMS, disease progression worsens steadily.
- The MS Society expects that treatment with siponimod may have the potential to allow people living with SPMS to remain in the workforce, sustain family and social roles and responsibilities longer, improve their quality of life, decrease the need for caregiving, and reduce the financial burden to health and social systems.

## Clinical Trials

The CADTH systematic review included one double-blind, randomized, event-driven, exposure-driven, phase III, placebo-controlled trial of patients with SPMS, the EXPAND study. A total of 1,651 patients with active (n = 779) and non-active (n = 872) SPMS were enrolled, including sites within and patients from Canada. To be eligible for inclusion, patients needed to have a history of RRMS and a current diagnose of SPMS, defined by a progressive increase in disability for at least six months, with or without relapses. Patients also had to have an EDSS score between 3.0 and 6.5 (inclusive) at screening, and documented progression in the two years prior to enrolment. Patients with various comorbidities and patients with homozygosity for the CYP2C9*3 were ineligible for the EXPAND study. Patients were randomized in a 2:1 ratio to either siponimod 2 mg or placebo. Randomization was stratified by region. The primary objective was to demonstrate the superiority of siponimod relative to placebo in terms of its ability to delay the time to three-month CDP, measured by the EDSS.

The trial was conducted in patients with a broad range of SPMS phenotypes, but the indication approved by Health Canada is for patients with SPMS with active disease. Data that were available to support the efficacy of siponimod for this patient population were limited to planned subgroup analyses that were conducted for the primary and key secondary outcomes of the EXPAND study as part of the original protocol. The subgroups of interest to this review following the indication for siponimod approved by Health Canada are those related to disease activity (i.e., patients with or without relapses and patients with or without gadolinium (Gd)-enhancing T1 lesions). In addition, the results of exploratory, post-hoc analyses of patients with active SPMS (N = 782), defined as patients with relapses in the two years prior to screening and/or at least one T1 Gd lesion at baseline, were also included. Patients with active SPMS included in this post-hoc subgroup analysis represented 47% of the overall study population.

In the overall study population, the discontinuation rate was 18.3% in the siponimod group (including 5 patients who were not exposed to study drug) and 22.3% in the placebo group. In the active SPMS subgroup, the percent of discontinuations in the placebo group was greater than in the siponimod group (27% and 18%, respectively). Limitations associated with the evidence of the overall EXPAND study include partial unblinding and high disproportional discontinuation. The subgroup analyses are subject to these limitations as well, in addition to a small sample size, potential for randomization that was not maintained due to lack of randomization stratification at baseline, and results that may only be considered exploratory as statistical testing, where conducted, was not controlled for multiplicity and therefore subject to potential inflated risk of type I error. In terms of external validity, patients with a variety of comorbidities and those with a baseline EDSS score greater than 6.5 were excluded from the EXPAND study, therefore limiting the generalizability of the study results to patients with more severe disease. The durability of long-term treatment effect and safety is unknown; therefore, the results as observed by month 12 may be limited in their applicability to chronic use of siponimod in clinical practice.

Finally, placebo as the sole comparator used in the pivotal trial for siponimod is a limitation of the evaluation of siponimod in the context of Canadian clinical practice. In the absence of treatment for SPMS, patients might be continued on treatment for RRMS when they progress to SPMS even if this only treats symptoms rather than the disease.

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following: disability progression, health-related quality of life (HRQoL), mobility, relapse-related outcomes, and imaging outcomes. The primary outcome in the EXPAND study was time to three-month CDP based on the EDSS score. Outcomes related to disease progression, HRQoL, mobility, cognitive function, and symptoms such as fatigue were identified as being important to patient groups; however, outcomes related to fatigue were not assessed in the EXPAND study and cognitive function was not assessed in the active SPMS population specifically.

- In the EXPAND study, disability progression was evaluated using the EDSS, an assessment of neurologic impairment in multiple sclerosis based on a neurological examination, which is performed by an independent EDSS rater. It is scored using an ordinal scale from zero to 10, where zero corresponds to no disability and 10 indicates death due to MS. Using this scale, CDP was defined using the minimal important difference (MID) for the EDSS, which was a one-point increase from baseline for patients who had a baseline EDSS score of 3.0 to 5.0, or a 0.5 point increase for patients who had a baseline score of 5.5 to 6.5. Limitations of the EDSS include moderate intra-rater reliability, poor assessment of upper limb and cognitive function, and lack of linearity between score difference and clinical severity.
- HRQoL was evaluated using three patient-reported outcome measures: the MS Walking Scale (MSWS-12), MS Impact Scale, and the EuroQol 5-Dimensions. Only the MSWS-12 at month 12 was analyzed in the subgroup of patients with active SPMS. The MSWS-12 (version 2) assesses the limitations on walking due to multiple sclerosis using 12 items that contribute to an overall score ranging from zero to 100, where a higher score indicates greater impairment. A range from 10.4 to 22 points was identified as the MID for the MSWS-12. High test-retest reliability, as well as convergent and discriminant validity, have been demonstrated in patients with MS.
- Mobility was assessed using the T25W. The T25W measures the number of seconds it takes a patient to walk 25 feet. The test is re-administered immediately by having the patient walk back to the starting point. Assistive devices may be used and there is a time limit of 180 seconds per trial. One of the key secondary outcomes in the EXPAND study was the time to three-month confirmed worsening of at least 20% from baseline in the T25W that was sustained for at least three months. A change of 20% in the T25W represents the MID for this outcome.
- The occurrence of relapses were reported as an annualized relapse rate (ARR) based on the number of confirmed MS relapses. A confirmed MS relapse was distinguished by an accompanying clinically relevant change in the EDSS score; however, the clinical experts on this review did not think that confirmation via EDSS score was necessary.
- MRI outcomes were included in the EXPAND study. The change from baseline in T2 lesion volume (at month 12 and month 24) was used as a proxy for burden of disease, and inflammatory disease activity was measured by the number of new or enlarging T2 lesions, the number of T1 Gd-enhancing lesions, and the percent of brain volume change from baseline.

## Efficacy

For the primary outcome in EXPAND (time to three-month CDP), in the overall population, an HR of 0.79 (95% CI, 0.65 to 0.95; P = 0.0134) was reported, corresponding to a 21.2% risk reduction for the time to three-month CDP with siponimod compared with placebo. In the planned subgroup analysis, the HR for patients with relapses in the two years prior to study start was 0.67 (95% CI, 0.49 to 0.91), and 0.87 (95% CI, 0.68 to 1.11) in patients without relapses. Furthermore, in patients with more than one Gd-enhancing T1 lesion at baseline, the HR was 0.64 (95% CI, 0.42 to 0.95), and 0.82 (95% CI, 0.66 to 1.02) in patients without Gd-enhancing T1 lesions at baseline. In the post-hoc active SPMS subgroup analysis, based on an HR of 0.69 (95% CI, 0.53 to 0.91; P = 0.0094), treatment with siponimod at a maintenance dose of 2 mg once daily corresponded to a 30.7% risk reduction in the time to three-month CDP compared to placebo. Of note, the absolute risk difference in the active SPMS subgroup for three-month CDP was [redacted] ([redacted] versus [redacted], siponimod versus placebo, respectively) and this difference was 5.4% in the overall patient population (26.3 versus 31.7%, siponimod versus placebo, respectively). The HR (siponimod to placebo) for time to six-month CDP was 0.63 (95% CI, 0.47 to 0.86) in the active SPMS subgroup, and 0.74 (95% CI, 0.60 to 0.92) in the overall population.

For the overall population, the between-group difference for the MSWS-12 converted score was –1.83 (95% CI, –3.85 to 0.19; P = 0.0764). For the post-hoc active SPMS subgroup analysis, the between-group difference for the MSWS-12 converted score was [redacted]. The reported results for the HRQoL outcomes did not meet the MID, which ranged from 10.4 to 22.

In the overall population, siponimod did not demonstrate superiority over placebo in time to three-month confirmed worsening in the T25W (HR = 0.94; 95% CI, 0.80 to 1.10; P = 0.4398). In addition, the planned subgroup analysis by disease activity status at baseline showed no difference between treatment groups in time to three-month confirmed worsening of at least 20% from baseline in T25W; nor was there a pattern of differential treatment effect by relapsing compared to non-relapsing or rapid evolving disease. In the post-hoc subgroup analysis of patients with active SPMS, an HR of 0.85 (95% CI, 0.68 to 1.07) for siponimod compared to placebo was reported for time to three-month confirmed worsening in the T25W. The absolute risk difference between siponimod and placebo was [redacted] in the active SPMS subgroup and [redacted] in the overall population.

In the overall population, the adjusted ARR for confirmed relapses was associated with a rate reduction of 55.5% (between-group ARR ratio of 0.445; 95% CI, 0.337 to 0.587; P < 0.0001). The sponsor-submitted post-hoc active SPMS subgroup analysis reported an ARR ratio of 0.544 (95% CI, 0.387 to 0.766, P = 0.0005) for confirmed relapses, which corresponds to a rate reduction of 45.6%.

In terms of change from baseline in T2 lesion volume at month 12, the analysis of the overall population showed a treatment difference of –613.1 $mm^3$ (95% CI, –800.2 to –426.0; P < 0.0001) in favour of siponimod; however, this result violated the statistical testing hierarchy due to the failure of the second ranked outcome (confirmed worsening of ≥ 20% from baseline on the T25W, which was not statistically significant). The planned subgroup defined by relapses in the two years prior to study start reported a treatment group difference of [redacted] and [redacted] in those without relapses. The post-hoc subgroup analysis of patients with active SPMS reported a treatment group difference of [redacted] in the change from baseline in T2 lesion volume at month 12.

## Harms (Safety)

Safety results were based on the overall EXPAND study population and not available by subgroup.

- Overall, adverse events (AEs) were higher among patients treated with siponimod (88.7%) than with placebo (81.5%). The incidence of specific AEs was similar between the two treatment groups, although hypertension was slightly more common for patients treated with siponimod (10.5% versus 7.5%), as was nausea (6.7% versus 3.5%), alanine aminotransferase increase (5.9% versus 1.5%), and peripheral edema (4.5% versus 2.4%).
- In the EXPAND study, serious AEs were reported by 17.9% of patients treated with siponimod and 15.2% of patients treated with placebo. The number of specific events reported was low and similar between treatment groups.
- The proportions of withdrawal due to AEs were low (7.6% for siponimod versus 5.1% for placebo). [redacted].
- Bradycardia and macular edema were identified as notable harms in the CADTH review protocol and were more common in the siponimod group compared with the placebo group (4.5% versus 2.6% and 1.6% versus 0.2%, respectively). Four deaths from each treatment group were reported during the EXPAND study.

## Indirect Treatment Comparisons

The sponsor submitted a MAIC that evaluated the efficacy of siponimod against interferon beta 1a and 1b, and natalizumab in patients with SPMS. Individual patient data from the EXPAND study were used to match and adjust patients to those included in the comparator interferon trials. MAIC was deemed necessary due to differences across trials in the patient populations enrolled and changes in the treatment paradigm. Pairwise comparisons between siponimod and natalizumab, as well as siponimod and different interferon beta products and doses, were conducted using MAIC methods. The results of some analyses suggest that disability progression may be delayed for siponimod versus interferon beta, while others found no differences. No differences were found between siponimod and natalizumab in terms of disability progression. In addition, no differences between treatments were found for the analyses of relapse rates, which showed wide CIs, suggesting there was considerable uncertainty in the results. There was no assessment of harms in the sponsor-submitted MAIC.

Although the methods used to conduct the MAIC followed technical guidance, the analyses have a number of limitations that impact their internal and external validity, including concerns regarding the overlap between the comparators and siponimod trial populations, and the availability of data to allow for matching and adjustment. Matching was not possible for all criteria, and for some analyses, no, or limited, adjustment to balance potential effect modifiers was feasible. The small effective sample size of many analyses confirms that substantial differences exist between the patient populations in the siponimod and comparator trials. Given these issues, there is substantial uncertainty in the results. Moreover, most patients included in the analyses did not have active SPMS, and the treatment effects reported for siponimod versus interferon apply to a patient population that is interferon naive. The utility of these data is limited as the analyses were not specific to patients with active SPMS (the approved indication for siponimod), and most patients who have developed SPMS would have previously received DMT.

## Cost and Cost-Effectiveness

Siponimod is available as 0.25 mg and 2 mg film-coated tablets. Treatment is initiated over five days: dose titration starts with 0.25 mg once daily on day 1 and day 2, followed by daily doses of 0.5 mg on day 3 (two tablets of 0.25 mg), 0.75 mg on day 4 (three tablets of 0.25 mg), and 1.25 mg on day 5 (five tablets of 0.25 mg), to reach the maintenance dose of 2 mg on day 6. If a titration dose is missed on one day during the first six days of treatment, treatment needs to be re-initiated. At the submitted prices of $22.39 per 0.25 mg and $89.32 per 2 mg tablet, the first-year cost of treatment is $32,444, and $32,622 annually thereafter.

The sponsor submitted a cost-utility analysis comparing siponimod, interferons (Extavia, Rebif, Avonex, Betaseron), natalizumab, and BSC for patients with active SPMS, in line with the Health Canada–approved indication for siponimod. The sponsor developed a Markov model to simulate the clinical course of disease progression through 10 health states: EDSS categories (0 to 9) and death. The analysis was based on an annual cycle length over a lifetime horizon (until patients reached 101 years of age). In each cycle, patients also experienced relapse (acute attacks of disease) according to an EDSS-score-specific rate. Patients discontinued treatment when they achieved an EDSS score of 7 or greater, and a proportion of patients were assumed to discontinue therapy based on other causes. Following discontinuation, patients switched to treatment with BSC.

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

- A number of issues regarding model validity, as well as errors in the model code, were identified. While the sponsor made the requested corrections, this greatly limited the degree of confidence in the model results.
- The comparative clinical effectiveness of siponimod versus interferons relied on a MAIC for patients with SPMS. Uncertainty exists as to whether these relative treatment effects would apply to patients with active SPMS.
- Inappropriate assumptions relating to mortality by EDSS led to an overestimation of the mortality risk associated with higher EDSS scores; thus, overestimated the benefit of slowing disease progression.
- Concerns were raised regarding the validity of the assumptions used to derive utility values by EDSS level. These assumptions likely overestimated the disutility associated with more severe disease states; thus, overestimated the benefit of slowing disease progression.
- The assumption of improving health status (i.e., a proportion of patients moving to an improved EDSS level) was not supported by the clinical experts consulted by CADTH.
- In the sponsor's base-case analysis, the relative effectiveness data for BSC were not based on an active SPMS population.
- Data relating to mortality, costs, utilities, and disease progression were not specific to an SPMS population; only baseline population characteristics and annual relapse rate by EDSS score were specific to an SPMS population.
- Only one DMT (natalizumab) was compared to siponimod. However, minimal details of the methods to inform relative efficacy estimates for this comparison were provided.

CADTH undertook a reanalysis that addressed issues relating to mortality, utility values, and improving health status for the comparison of siponimod versus BSC, but was unable to address concerns relating to data that were not specific to an active SPMS population.

Siponimod was associated with incremental QALYs of 0.75 and incremental health care costs of $146,424, leading to an ICER of $194,007 per QALY when compared with BSC. At a $50,000-per-QALY threshold, a 63% price reduction would be needed for siponimod to be considered cost-effective.

## 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.

## June 17, 2020 Meeting

## Regrets

One CDEC member did not attend.

## Conflicts of Interest

None