CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

SIPONIMOD (MAYZENT)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Secondary-progressive multiple sclerosis

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Abbreviations

BSC	best supportive care
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
ICER	incremental cost-effectiveness ratio
IFN	interferon
MAIC	matching-adjusted indirect comparison
MS	multiple sclerosis
QALY	quality-adjusted life-year
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary-progressive multiple sclerosis
WTP	willingness-to-pay

Table 1: Summary of Sponsor's Economic Submission

Drug product	Siponimod (Mayzent) 2 mg tablet
Study question	What is the incremental cost-effectiveness of siponimod for the treatment of SPMS with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability, as compared to IFNs, best supportive care, and natalizumab in Canada?
Type of economic evaluation	Cost-utility analysis
Target population	Adults with SPMS with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability in Canada
Treatment	Siponimod 2 mg daily after initiation
Outcome	QALYs
Comparators	• IFNs (Extavia, Rebif, Avonex, Betaseron) • Natalizumab • BSC (consisting of pharmacological and non-pharmacological management that the adult will receive to manage SPMS symptoms)
Perspective	Canadian public health care payer
Time horizon	Lifetime (53 years)
Results for base case	• Siponimod was more costly and more effective compared to IFNs and BSC, and less costly and more effective when compared to natalizumab. IFNs and natalizumab were subject to dominance or extended dominance. The ICER for siponimod compared to BSC was $102,328 per QALY. • In a secondary analysis based on the EXPAND active subgroup, the ICER for siponimod compared to BSC was $154,550 per QALY, with a 2.9% probability that siponimod was cost-effective at a WTP threshold of $50,000 per QALY.
Key limitations	• CADTH identified a number of limitations regarding model validity and a number of errors in the model coding, which required a number of requests for the sponsor to make corrections. This greatly limited the degree of confidence in the model results. • The comparative effectiveness of siponimod vs. IFNs relied on a matching-adjusted indirect comparison relating to all adults with SPMS that CADTH considered provided too much uncertainty with respect to the relative treatment effects for adults with active disease. • Inappropriate assumptions relating to mortality by EDSS led to an overestimation of the mortality risk associated with higher EDSS scores and 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 and thus overestimated the benefit of slowing disease progression. • The assumption of improving health status (i.e., a proportion of adults moving to an improved EDSS level) was not supported by the clinical experts consulted by CADTH. • In the sponsor's base analysis, the relative effectiveness data for BSC is inappropriate and not based on an active SPMS population. • Data relating to mortality, costs, utilities, disease progression, and treatment efficacy were not specific to a SPMS population. Only baseline population characteristics and annual relapse rate by EDSS score were specific to a SPMS population.

	• Only 1 DMT, natalizumab, was compared to siponimod. However, minimal details of the methods to inform relative efficacy estimates for this comparison were provided.
CADTH estimate(s)	• CADTH addressed the issues relating to mortality, utility values, and improving health status. • In the CADTH base case, siponimod compared with BSC 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. • The results should be viewed with extreme caution given the lack of data for adults with active disease included in the analysis and the lack of face validity with the results. CADTH concluded that all analyses relating to the cost-effectiveness of siponimod vs. IFNs or natalizumab included too much uncertainty to be considered credible.

BSC = best supportive care; DMT = disease-modifying therapy; EDSS = Kurtzke Expanded Disability Status Scale; ICER = incremental cost-effectiveness ratio; IFN = interferon; QALY = quality-adjusted life-year; SPMS = secondary-progressive multiple sclerosis; vs. = versus; WTP = willingness-to-pay.

Drug	Siponimod (Mayzent)
Indication	For the treatment of adults with secondary-progressive multiple sclerosis with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	0.25 mg and 2 mg oral tablets
NOC date	February 20, 2020
Sponsor	Novartis Pharmaceuticals Canada Inc.

Executive Summary

Background

Siponimod (Mayzent) is a sphingosine 1-phosphate receptor modulator.[1] This submission relates to the Health Canada–approved indication for the treatment of adults with secondary-progressive multiple sclerosis (SPMS) with active disease, evidenced by relapses or imaging features characteristic of multiple sclerosis (MS) inflammatory activity, to delay the progression of physical disability.[2] Siponimod is available as 0.25 mg and 2 mg film-coated tablets.[1] Treatment has to be initiated over five days: dose titration starts with 0.25 mg once daily on day 1 and day 2, followed by once 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 siponimod. 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 costs of treatment are $32,444 and $32,622 annually thereafter.

Prior to Health Canada approval and the determination of the indication, the sponsor submitted a cost-utility analysis based on a Markov state-transition model comparing siponimod with interferons (IFNs) (Extavia, Rebif, Avonex, and Betaseron) in adults with SPMS.[2] On request, the sponsor provided a model that included best supportive care (BSC) to fully explore the cost-effectiveness of siponimod.[3] BSC consists of therapies used to control SPMS symptoms and does not include therapies that would alter disease progression. These non-pharmacological therapies that are used to manage SPMS symptoms would also be received by those who are receiving siponimod. Following Health Canada approval for siponimod restricted to adults with active disease, the sponsor submitted an additional analysis with revised parameter estimates and inclusion of natalizumab as a further comparator.[4]

In the model, adults transitioned between Kurtzke Expanded Disability Status Scale (EDSS) states 0 through 9 within SPMS. In each cycle, adults can transition to the death state, with the probability of death varying by EDSS score. In addition, in each cycle, the model estimated the proportion of adults experiencing relapse. The annualized relapse rate was assumed to vary by EDSS score. The analysis was run over a lifetime time horizon (up to an age of 101 years) using an annual cycle length. The analysis adopted a Canadian public payer health care system perspective.

Baseline adult characteristics and data on natural history with respect to both the progression of adults between EDSS states and the annualized relapse rates were derived from the EXPAND trial.[5] However, only adult characteristics and the annualized relapse rates were based on adults with active disease from this trial. The effect on natural history (progression and relapse) of siponimod compared to each individual IFN was derived from a sponsor-conducted matching-adjusted indirect comparison (MAIC). Within the submission, an additional model comparing siponimod to BSC was provided whereby efficacy estimates specific to active SPMS were used. However, this was not used in the sponsor's base case. Instead, the efficacy estimates for BSC from the MAIC were used, which are not specific to active disease. For the comparison with natalizumab, an indirect treatment comparison based on the ASCEND and EXPAND studies was conducted without adjustment for differences in adult populations.

Treatment was assumed to stop once adults reached EDSS 7. In addition, an all-cause discontinuation rate was applied, based on the EXPAND data for siponimod, with a relative risk based on an indirect treatment comparison applied to this for each of the IFNs and natalizumab. Adverse events with treatment were included in terms of their effect on cost and utility values. Costs by EDSS state were derived from a CADTH therapeutic review and were based on costs from a Canadian report for RRMS.[6] Utility values for EDSS states 3 to 7 were derived from the EXPAND trial. For EDSS states 0, 1, 2, 8, and 9, data from a previous study were used.[2,7]

The sponsor reported that siponimod was more costly and more effective than all IFNs. In a sequential analysis of natalizumab, Extavia, Betaseron, Rebif, and Avonex were subject to dominance or extended dominance compared with siponimod and BSC. The incremental cost-effectiveness ratio (ICER) for siponimod versus BSC was $102,328 per quality-adjusted life-year (QALY). The probability that siponimod was cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY was 2.9% (as reported by the model). The probability that siponimod was cost-effective when only considering natalizumab and IFNs, given a WTP threshold of $50,000 per QALY, was 50%.

Summary of Identified Limitations and Key Results

CADTH identified the following limitations relating to the sponsor's economic model.

A major limitation with the sponsor's analysis is that the only data specific to active disease, which is the target population of the analysis (i.e., indication), are the baseline adult characteristics and the annualized relapse rates. Further, the analysis comparing siponimod to BSC in the sponsor's base case did not include treatment efficacy data related to the active disease population. A model that was subsequently provided based on CADTH's request included this data but other parameters, such as disease progression, were not revised to reflect the active SPMS population. Thus, the submitted analysis does not reflect the target population (active SPMS) and should be considered exploratory in nature.

The results of the model suggest that the expected values for QALYs for all comparators were higher for adults with active disease than for all adults with SPMS. This implies that adults with active SPMS have better health outcomes than those who do not have active disease. There is a high degree of uncertainty as to the clinical validity of this finding. Although clinically some adults with active disease may have less progressed disease, data used within the model suggests that EDSS scores are similar between active and non-active SPMS. Given adults with active disease have more relapses, one could expect them to have

poorer health outcomes. This could suggest that additional health gains derived from siponimod may have been overestimated in the analysis.

Issues were also identified with the sponsor's choice of inputs, specifically the mortality data. Data for mortality was derived from a study by Pokorski et al.[8] that was a re-reporting of an original study by Sadovnick et al.[9] The original study provided excess mortality calculations for adults with mild, moderate, and severe MS, defined using EDSS scores of 0 to 3.5, 4 to 7, and 7.5 and higher, respectively. From this, the sponsor derived mortality multipliers for an individual EDSS score as employed in previous submissions. This approach was deemed inappropriate due to the lack of transparency as to how values were derived, given that the study by Sadovnick et al. specifies that further breakdown by EDSS could not be achieved with the limited data analyzed. Reanalysis therefore adopted the actual data from the study by Sadovnick et al.[9]

The model allowed for an improvement in EDSS state within a cycle; for some states, the annual probability of improvement exceeded 35%. The clinical experts consulted by CADTH for this review did not accept that this was likely. Reanalysis excluded the probability of health status improvement.

Utility values for EDSS states 3 to 7 were derived from the EXPAND trial through a regression analysis approach.[5] Utility values for EDSS 0, 1, 2, 8, and 9 were derived from a previous study by Orme et al.[7] CADTH had concerns with the approach adopted, and the inconsistencies between values used within the model compared to values presented in the sponsor's submitted technical report. CADTH used the values for EDSS values 3 to 7 as presented in the report and revised utility values for EDSS 8 and 9 were adopted.

The original economic submission included only a comparison of siponimod with IFNs, but excluded BSC.[2] Based on the CADTH clinical reviewers and clinical experts consulted by CADTH, BSC was considered a relevant comparator, even in the active SPMS population. Upon CADTH request, the sponsor submitted a revised model to allow a comparison of siponimod to BSC based on the EXPAND clinical data;[5, 10] however, the sponsor maintained the stance that BSC was an inappropriate comparator. The MAIC used to inform IFN evidence was also of limited use. The CADTH Clinical Review Report concluded that "there are considerable limitations to the validity of the findings of the MAIC, including that the analyses were not specific to adults with active SPMS, which makes the utility of these data poor."

Natalizumab was the only disease-modifying therapy (DMT) included in the analysis. The reporting of the methods for the clinical efficacy relating to natalizumab versus siponimod was limited, suggesting that such results should be considered exploratory.

CADTH conducted detailed reanalysis focusing on the comparison of siponimod to BSC based on the EXPAND trial, adopting more appropriate mortality multipliers, using revised utility data, and assuming no improvement in health status over time.

Conclusions

In the revised submission pertaining to active SPMS, CADTH considered the estimates of comparative clinical efficacy for siponimod compared to IFNs and natalizumab to be too uncertain to be useful.

Based on CADTH reanalyses, compared to BSC, siponimod led to an increase in QALYs of 0.75 and incremental health care costs of $146,424, resulting in an ICER of $194,007 per QALY. There was a 0% chance that siponimod would be cost-effective at a $50,000 per QALY threshold. At this threshold, a 63% price reduction would be needed for siponimod to be considered cost-effective.

Given the limitations identified with the economic model that could not be addressed by CADTH — technical issues with the model, the limited applicable data, and concerns regarding face validity — the results must be considered with extreme caution as they may not reflect the likely ICER of siponimod for the treatment of active SPMS.

Information on the Pharmacoeconomic Submission

Summary of Sponsor's Pharmacoeconomic Submission

In the sponsor's original submission pertaining to the full SPMS adult population, the sponsor submitted a cost-utility analysis based on a Markov state-transition model comparing siponimod with IFNs (Extavia, Rebif, Avonex, and Betaseron).[2] On request, the sponsor provided a model that facilitated a comparison of siponimod with BSC.[3] Following Health Canada's approval for siponimod to be indicated for adults with active SPMS, the sponsor submitted a revised report where certain parameter estimates were updated and natalizumab was included as a comparator.[4] All methods and results in this report pertain to the revised analysis that looks exclusively at patients with active SPMS, as per the Health Canada indication.

In the model, patients transitioned between EDSS states 0 through 9 within SPMS. In each cycle, patients can transition to the death state, with the probability of death varying by disease severity. In addition, in each cycle, the model estimated the proportion of adults experiencing relapse. The annualized relapse rate was assumed to vary by EDSS score. The analysis was run over a lifetime time horizon (up to an age of 101 years) using an annual cycle length. The analysis incorporated a discount rate of 1.5% per annum and was conducted from the perspective of the Canadian publicly funded health care system.

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of adults with SPMS receiving treatment either with siponimod, IFNs (Extavia, Rebif, Avonex, and Betaseron), or natalizumab. The model was based on adults transitioning across EDSS states 0 to 9 and death and incorporated an annualized rate of relapse. The sponsor adopted a cycle length of one year. Adults with SPMS entered the model in a state between EDSS 2 and 7. In each cycle, patients could transition between EDSS states or enter the absorbing death state. It was assumed that adults who reached an EDSS score of 7 or greater while on treatment would discontinue treatment. In addition, annually, a proportion of adults in other EDSS states were assumed to discontinue therapy based on other causes. Following discontinuation, patients switched to treatment with BSC with transition probabilities between EDSS states informed by data from the placebo arm of the EXPAND trial. The probability of death from EDSS states was based on general population mortality adjusted by EDSS state-specific mortality multipliers.

Model Inputs

Baseline patient characteristics on entry into the model related primarily to adults with active SPMS in either the BSC and siponimod arms of the EXPAND trial.[5] The age of the patient population was assumed to be 46.55 years and the population was distributed across EDSS states (EDSS 2 = 0.64%, EDSS 3 = 8.61%, EDSS 4 = 17.87%, EDSS 5 = 17.22%, EDSS 6 = 55.53%, and EDSS 7 = 0.13%).

For adults receiving treatment with siponimod or IFN, the natural history data were adjusted by a relative treatment effect for both progression and relapse rates, derived from a sponsor-backed MAIC.[2] The analysis involved comparing siponimod to each IFN individually by matching the EXPAND patient dataset to the trials for each IFN versus placebo, based on a list of possible treatment effect modifiers. This required reducing the effective sample size to

between 28% and 39% of the overall EXPAND population. This allowed estimation of the effect of the IFN versus placebo and siponimod versus placebo for each MAIC comparison. These were then pooled based on choosing one IFN (Extavia) as a base comparator. This analysis was not specific to adults with active SPMS. After discontinuing treatment with siponimod or IFNs, patients were assumed to experience the same transition probabilities as those on BSC.

For adults on BSC, transition probabilities between EDSS states were derived from all patients in the placebo arm of the EXPAND clinical trial.[5] In the sponsor's base-case analysis, the relative efficacy of siponimod versus BSC was based on the MAIC and was therefore not specific to active disease. However, an estimate of relative efficacy derived from the active SPMS subgroup of the EXPAND study was provided.

For natalizumab, both the relative discontinuation rate versus siponimod and the comparative effectiveness in terms of annualized relapse rates and disease progression were obtained through an indirect treatment comparison based on the EXPAND and ASCEND studies.[5, 11] The report provided only limited details on how this was conducted.

The probability of mortality was based on adjusting all-cause mortality data for the Canadian general population to provide a probability of death specific to each EDSS state.[12] Mortality associated with EDSS state was estimated by multipliers, which were stated in the written report as to be derived from a report by Pokorski et al.[8]

Health state utilities in the model were based on disease severity (as measured by EDSS) and were obtained from both the EXPAND trial dataset and a previous study by Orme et al.[5, 7] Utility values for EDSS states 3 to 7 were derived from the EXPAND trial through a regression analysis approach. Full details of this analysis were not provided. Utility values for EDSS 0, 1, 2, 8, and 9 were derived from the study by Orme et al.[7] A disutility for a relapse was derived from the EXPAND trial.[5]

Costs for comparator therapies were detailed in the report, though no sources were provided. Drug administration and monitoring costs were included; they were based on consultation with Canadian clinicians and unit costs for Ontario were applied.[13-15] Adverse event management costs were included, though full details of how they were derived were not included in the report. Costs for patient management by EDSS state and for relapses were derived from a CADTH therapeutic review for relapsing-remitting MS (RRMS) and adjusted to 2019 Canadian dollars.[6]

The analysis did not incorporate active SPMS-specific data relating to disease progression by EDSS level, mortality, relative treatment effect of siponimod versus IFNs or natalizumab, treatment discontinuation rates, and health state utility values.

Sponsor's Base Case

The sponsor's base case compared siponimod to IFNs, natalizumab, and BSC. However, as mentioned earlier, analysis pertaining to BSC did not use data from the EXPAND trial relating to the active disease population.

The sponsor reported that siponimod was less costly and more effective than natalizumab, and more costly and more effective than all IFNs and BSC (see Table 2). The incremental QALY gain ranged from 1.31 to 1.67 and the difference in health care costs ranged from a savings of $66,291 to additional costs of $147,818. The ICER for siponimod versus IFNs ranged from $7,765 to $41,006 per QALY, and the ICER for siponimod versus BSC was

$102,328 per QALY. In a sequential analysis, all comparators other than siponimod and BSC were subject to dominance or extended dominance.

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

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. Extavia	Sequential incremental cost per QALY gained
Non-dominated therapies						
BSC	615,224		5.78			
Siponimod	763,042	147,818	7.23	1.44	102,328	102,328
Dominated therapies						
Extavia	709,017	93,794	5.91	0.13	738,191	Subject to extended dominance
Betaseron	715,705	100,481	5.91	0.13	766,058	Subject to extended dominance
Rebif 22	740,701	125,478	5.39	–0.40	Dominated	Dominated
Avonex	748,742	133,519	5.39	–0.40	Dominated	Dominated
Natalizumab	829,333	214,109	5.56	–0.23	Dominated	Dominated

BSC = best supportive care; QALY = quality-adjusted life-year; vs. = versus.

Note: All costs are presented in 2019 Canadian dollars. Interferon beta-1b (Extravia and Betaseron); interferon beta-1a (Avonex, Rebif 22).

Source: Total costs and QALYs are probabilistic values, based on an economic model submitted to CADTH on March 25, 2020.[2]

It should be noted that the sponsor did provide a model that included the comparison with BSC based on active SPMS data from the EXPAND trial. However, this analysis was not included in the written report. In the model submitted by the sponsor, the incremental cost per QALY gained for siponimod versus BSC was $154,550 per QALY, with a 2.9% probability that siponimod was cost-effective if the WTP threshold was $50,000 per QALY.

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted a range of probabilistic scenario analyses that were in the written report, based on the revised model reported in Table 2. In all analyses, IFNs and natalizumab remained subject to dominance or extended dominance and the incremental cost per QALY for siponimod versus BSC gain ranged from $78,742 to $600,698. However, CADTH had significant concerns with the applicability of the sponsor's base-case analysis, which similarly applies to all sensitivity analyses.

Limitations of Sponsor's Submission

CADTH identified the following limitations with the sponsor's model:

- **Technical Issues With Model:** The original submitted model had 87,792 IFERROR statements. IFERROR statements are problematic in that they should generally be unnecessary within a model. If included, it makes the task of ensuring the validity of the model more difficult. CADTH made several requests to remove these statements, such that model testing could be facilitated (4,381 statements remained in the model). The sponsor argues this is necessary for conducting the probabilistic analysis. CADTH disagrees that IFERROR statements should be necessary if the model is coded

appropriately, as this implies that the probability distributions used are incorrectly specified and may not be truly reflective of the uncertainty within given parameters, or could be masking other issues in the model. There were also 467 IFERROR statements in other worksheets, including those containing the Markov trace for both siponimod and BSC. Thus, CADTH is concerned regarding the validity of the model and notes that the results presented should be treated with a degree of caution.

CADTH also noted that the characterization of uncertainty with respect to costs, utilities, mortality, discontinuation, and transition probabilities were not reflective of the sample data from which they were obtained. CADTH also notes that the unnecessary complexity of the model makes review of the model challenging and that CADTH continues to note minor errors throughout the model.

- **Inappropriate Data for Subgroup-Specific Analysis**: Although the submission purports to be specific to the active disease subgroup, only limited data specific to this subgroup were employed within the analysis. Active disease-specific data related solely to the annualized relapse rate by EDSS level and baseline patient characteristics with respect to age, weight, gender, and baseline EDSS. As noted earlier, the analysis did not incorporate active SPMS-specific data relating to disease progression by EDSS level, mortality, relative treatment effect of siponimod versus IFNs or natalizumab, treatment discontinuation rates, and health state utility values. This limitation is particularly concerning in relation to the comparative effectiveness of siponimod versus IFNs and natalizumab. CADTH felt that this issue compounded with the concerns raised previously relating to the MAIC suggests that there is too great a level of uncertainty regarding the relative effectiveness of siponimod versus IFNs and natalizumab to consider the analysis and model appropriate for consideration of the relative effectiveness and cost-effectiveness of siponimod. CADTH concluded that, given the lack of relevant data combined with the technical issues with the model, there is insufficient basis to assess the cost-effectiveness of siponimod in active SPMS compared to IFNs and DMTs.
- **Lack of Face Validity of the Study Results**: Of concern is that the results of the sponsor's submission suggest that life expectancy and QALYs are greater for adults with active SPMS than non-active SPMS. The model estimates expected QALYs for siponimod for active SPMS as 7.23 compared to 7.16 for all adults with SPMS. There are similar findings for IFNs as well. Thus, the results could lack face validity, suggesting a further basis to conclude that there is too great a level of uncertainty with the submitted results for active SPMS to provide a confident conclusion about cost-effectiveness.
- **Choice and Handling of Mortality Data:** Data for mortality was derived from a report by Pokorski et al.; it was a re-reporting of data from a study by Sadovnick et al. that was not explicit to SPMS and likely featured predominantly adults with RRMS.[8] The study provided excess mortality calculations for adults with mild, moderate, and severe MS. From this, mortality multipliers were obtained by EDSS score. There are significant concerns over how these mortality multipliers were derived. One concern is the temporal nature of the data since the data relates to the period 1972 to 1985. Changes in symptom management over time may lead to questions regarding the relevance of data that relates to a period where the care of adults with MS may have been significantly different. One of the CADTH clinical experts suggested that there may now be limited increased mortality with MS. An additional concern, however, is how the data were analyzed. The original data for Sadovnick et al. suggest a mortality multiplier of 1.6 for EDSS scores between 0 and 3.5, 1.84 for EDSS scores between 4 and 7, and 4.44 for EDSS scores of 7.5 or greater. The submission includes an assumption whereby mortality multipliers for individual EDSS states are derived based on a predictive function that the sponsor says is premised on the

Pokorski et al. study.[8] No details of that function are provided. In the original Sadovnick et al.[9] article, it is stated that such analysis was not broken down in more detail due to the limited number of cases analyzed. Thus, it is unclear how such data were derived. CADTH adopted an approach whereby the multipliers by EDSS category were used as reported in the original article by Sadovnick et al.[9]

- **Assumed Improvement in Health Status:** Transition probabilities relating to disease progression (movement through EDSS states) were derived from the placebo arm of the EXPAND clinical trial.[5] The model allowed for an improvement in EDSS state within a cycle. For example, for adults in EDSS state 7, there is an annual probability of improvement in EDSS greater than 35% with BSC, with a 29% probability of remaining in EDSS level 7, and a probability of a decline in EDSS state of 36%. Based on the sponsor's model, within a cohort of adults starting at EDSS 6, by year 10, 36.4% of the adults still on siponimod would be in lower EDSS states than their initial state, with 9.83% in EDSS 2 or EDSS 3. This is exacerbated within the probabilistic analysis in that the use of prior distributions allows patients to transition from any EDSS state to another level — theoretically from EDSS level 9 to EDSS level 1. The clinical experts consulted by CADTH for this review did not accept that this was likely.

  Reanalysis excluded the probability of health status improvement and assumed patients could either remain at their current level or the disease could progress by up to three levels. For example, for adults in EDSS state 7, the annual probability of remaining in EDSS level 7 on BSC was 64% and the probability of a decline to EDSS state 8 or 9 was 36%.

- **Utility Values:** Utility values for EDSS states 3 to 7 were derived from the EXPAND trial through a regression analysis approach.[5] Details of this are limited and CADTH would be concerned if, in this analysis, EDSS was considered as having interval properties, meaning that the decrease in utility from EDSS 1 to EDSS 2 is the same as that of EDSS 8 to EDSS 9.

  Utility values for EDSS scores 0, 1, 2, 8, and 9 were derived from a previous study by Orme et al.[7] Using these values, the sponsor assumed utility values for EDSS 8 and EDSS 9 of –0.094 and –0.24, respectively. These values lacked face validity given the utility value for EDSS 7 was 0.42 — meaning a decline in utility value of 0.51 from EDSS 7 to EDSS 8. Likewise, the study by Orme et al. demonstrated much lower EQ-5D values for all states on average, compared to what was seen from the EXPAND trial. The study by Orme et al. reported a decline in utility from EDSS 7 to EDSS 8 of 0.346 and from EDSS 7 to EDSS 9 of 0.492. These incremental decreases were applied to the utility for EDSS 7 in the model to derive utility values for EDSS 8 and 9 of 0.074 and –0.072, respectively. It should be noted that the revised value of 0.074 for EDSS 8 is slightly higher than what the sponsor previously used, but closely corresponds with the raw data for EDSS 8 (0.077) from the EXPAND trial.

  CADTH noted that the utility values for EDSS states 3 to 7 in the model submitted in February 2020 are different than the values from the original submission and written report. The new model assigns higher values to better states, which would make results more favourable toward siponimod. Given there were no explanations provided for this change, CADTH adopted the values from the original model that are outlined in the sponsor's report.

- **Error on the Confidence Interval Relating to Relapse Rates:** The estimated relative relapse rate for BSC versus natural history was 1 yet the confidence interval for this was specified as 0.48 to 0.88. This is not feasible. CADTH set the confidence interval to 0.99 to 1.01.
- **Choice of Comparators**: Natalizumab was the only DMT comparator provided in the analysis. In clinical practice there are a variety of DMTs that patients with active SPMS may be placed on and therefore the cost-effectiveness of siponimod compared to these therapies remains unknown. Comparative efficacy of siponimod versus other DMTs was requested by CADTH; however, the sponsor acknowledged that there was no evidence or data available in the public domain, enabling either direct (clinical trials) or indirect comparisons to be made.

CADTH Reanalyses

As noted in the limitations, CADTH identified several important shortcomings relating to the sponsor's model. CADTH presents a revised probabilistic analysis (CADTH base case) comparing siponimod to BSC in Table 3 with alterations based on these limitations. The influence of each revision on the model results is presented in Table 14. The modifications made to the sponsor-submitted model include the following:

- In the original article by Sadovnick et al., the actual mortality multipliers were as follows: for EDSS levels 0 to 3.5, a multiplier of 1.60 (33/20.67); for EDSS levels 4 to 7, a multiplier of 1.84 (58/31.51); and for EDSS levels greater than or equal to 7.5, a multiplier of 4.44 (24/5.41). The CADTH base-case analysis used these values (see Table 11).
- Based on the input of the CADTH clinical experts, no improvement in EDSS was allowed. In the CADTH base case, there was no assumption of improvements in EDSS levels. Thus, the transition probability matrix for BSC was revised whereby the probability of remaining in the current EDSS level was assumed to be the sum of the original probability of staying in this level plus all previously assumed transitions to lower EDSS levels (see Table 12).
- The CADTH base case used the original utility values for EDSS states 3 to 7 and revised utility values for EDSS 8 and EDSS 9 based on the disutility of these states from the study by Orme et al. (EDSS = **Kurtzke Expanded Disability Status Scale.**

Source: Sponsor-submitted pharmacoeconomic evaluation report.

- Table 13). For EDSS level 8, the CADTH base case adopted a value of 0.074. This was calculated by taking the original utility value for EDSS level 7 from the EXPAND study (0.204) and deducting the difference in disutility from EDSS levels 7 and 8 from the study by Orme et al. (0.346 [0.252 to –0.094]). Similarly, for EDSS level 8, the CADTH base case adopted a value of –0.072. This was calculated by taking the utility value for EDSS level 8 derived earlier (0.074) and deducting the difference in disutility from EDSS levels 8 and 9 from the study by Orme et al. (0.146 [–0.094 to –0.024]).
- The 95% confidence interval for the relative relapse rate for BSC versus natural history was set to 0.99 to 1.01.
- Evidence related to IFNs and natalizumab was derived from a very limited analysis that was also not based on clinical data related to active SPMS. The CADTH Clinical Review Report concluded that "there are considerable limitations to the validity of the findings of the MAIC, including that the analyses were not specific to adults with active SPMS, which makes the utility of these data poor." Given this, along with other issues described earlier,

results related to these comparators were considered too uncertain to provide any value. Therefore, the CADTH base case only considers the cost-effectiveness of siponimod versus BSC.

Based on these revisions, the CADTH base case (see Table 8) suggests that siponimod for adults with SPMS is not a cost-effective treatment, at $50,000 per QALY threshold, at the sponsor-submitted price. The incremental cost per QALY gained for siponimod versus BSC was estimated to be $194,007 with the probability that siponimod is cost-effective, being 0% and 2% for WTP thresholds of $50,000 and $100,000 per QALY, respectively. Thus, if a decision-maker is unwilling to pay more than $194,007 for each QALY gained, BSC is the optimal therapy.

Table 3: CADTH Base Case — Revised Submission

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. BSC
BSC	717,886		5.41		
Siponimod	864,310	146,424	6.17	0.75	194,007

BSC = best supportive care; QALY = quality-adjusted life-year; vs. = versus.

Note: All costs are presented in 2019 Canadian dollars.

Source: Total costs and QALYs are based on a revised economic model founded upon changes outlined to CADTH on March 25, 2020. The total costs and QALYs incorporate corrections in the revised economic model.[16, 17]

It should be noted that as for the sponsor's submission, CADTH found that the expected values for QALYs for both BSC and siponimod were greater for adults with active SPMS (5.41 and 6.17, respectively) compared to all adults with SPMS (5.39 and 5.89, respectively) as shown in Table 16. CADTH also noted that significant QALY gains associated with siponimod were dependent on there being no treatment waning effect as shown in Table 17.

CADTH reanalysis with respect to price reductions should be considered with extreme caution. Analysis suggested that a price reduction of 63% would be required for siponimod to be cost-effective at a WTP threshold per QALY of $50,000 (see Table 9).

Table 4: CADTH Reanalysis Price Reduction Scenarios

Incremental cost per QALY gained ($) for siponimod vs. BSC		
Price	**Based on sponsor's base case**	**Based on CADTH base case**
Submitted	$154,550	$194,007
10% reduction	$135,582	$171,070
20% reduction	$116,614	$148,133
30% reduction	$97,647	$125,196
40% reduction	$78,679	$102,258
50% reduction	$59,712	$79,321
60% reduction	$35,054	$56,384
70% reduction	$21,776	$33,447
80% reduction	$2,809	$10,510
90% reduction	Siponimod dominates BSC	Siponimod dominates BSC

BSC = best supportive care; QALY = quality-adjusted life-year, vs. = versus.

Patient Input

The Multiple Sclerosis Society of Canada provided input for this review. Their feedback was based on survey responses predominantly from people diagnosed with SPMS and those affected by SPMS. Some respondents were diagnosed with RRMS.

The patients expressed desire for slow disease progression as one of the overarching goals of SPMS treatment. This outcome may help to minimize SPMS-related impacts on quality of life. The patients reported that these included a loss of independence, inability to participate in physical activity, increased caregiver burden, isolation, cognitive decline, decreased mobility, and inability to maintain employment.

The submitted model accounted for some, but not all, of the factors that characterized siponimod's value for money from a societal perspective. Namely, the sponsor included loss of productivity costs for the patient and caregiver. The sponsor did not explore other aspects identified in patient input (e.g., caregiver burden, out-of-pocket consequences due to cognitive decline, and increased mobility challenges), which could have been incorporated into a scenario analysis from the societal perspective.

Conclusions

In the revised submission pertaining to active SPMS, CADTH considered the estimates of comparative clinical efficacy for siponimod compared to IFNs and natalizumab to be too uncertain to be useful.

Based on CADTH reanalyses, compared to BSC, siponimod led to an increase in QALYs of 0.75 and incremental health care costs of $146,424, resulting in an ICER of $194,007 per QALY. There was a 0% chance that siponimod would be cost-effective at a $50,000 per QALY threshold. At this threshold, a 63% price reduction would be needed for siponimod to be considered cost-effective.

Given the limitations identified with the economic model that could not be addressed by CADTH — technical issues with the model, the limited applicable data, and concerns regarding face validity — the results must be considered with extreme caution as they may not reflect the likely ICER of siponimod for the treatment of active SPMS.

Appendix 1: Cost Comparison

The comparators presented in the following table 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 also 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 Cost Comparison Table for the Treatment of Secondary-Progressive Multiple Sclerosis

Drug/ comparator	Strength	Dose form	Price ($)	Recommended dosage	Average weekly drug cost ($)	Average annual drug cost ($)
Siponimod (Mayzent)	**0.25 mg 2 mg**	**Tablet**	**22.3285[a] 89.3150[a]**	**2 mg once daily[b]**	**Week 1: 447 Subsequent weeks: 625**	**Year 1: 33,444 Subsequent years: 32,622**
Injectable therapies indicated for treatment of SPMS						
Interferon beta-1a (Avonex)	30 mcg/0.5 mL (6 MIU)	Pre-filled syringe/pen	447.6100	30 mcg IM once weekly	448	23,356
Interferon beta-1b (Betaseron)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	110.0000	0.25 mg (8 MIU) SC every other day	440	22,089
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	103.8640	0.25 mg (8 MIU) SC every other day	415	18,968
Interferon beta-1a (Rebif)	22 mcg/0.5 mL (6 MIU) 44 mcg/0.5 mL (12 MIU) 66 mcg/0.5 mL (18 MIU) 132 mcg/0.5 mL (36 MIU)	Pre-filled syringe, cartridge, or pen	139.4640 169.7830 418.3844 509.3384	22 mcg to 44 mcg SC 3 times weekly	418 509 1,255 1,528	21,832 26,578 65,494 79,732
Injectable therapies currently used off-label to treat SPMS						
Glatiramer acetate (Glatect)	20 mg/mL	Pre-filled syringe	32.4000	20 mg SC once daily	227	11,834
Oral therapies currently used off-label to treat SPMS						
Dimethyl fumarate (Tecfidera)	120 mg 240 mg	Capsule	17.4925 34.9852	120 mg twice daily; after 7 days, increase to 240 mg twice daily	Week 1: 245 Subsequent weeks: 490	Year 1: 25,312 Subsequent years: 25,557
Fingolimod (Gilenya)	0.5 mg	Capsule	73.9100	0.5 mg once daily	517	26,996

Drug/ comparator	Strength	Dose form	Price ($)	Recommended dosage	Average weekly drug cost ($)	Average annual drug cost ($)
Teriflunomide (Aubagio)	14 mg	Tablet	58.3114	14 mg once daily	408	21,299
Cladribine (Mavenclad)	10 mg	Tablet	3,082.7000[c]	1.75 mg/kg body weight per year taken over 2 weeks, for 2 years	830	43,158
Infusion therapies currently used off-label to treat SPMS						
Alemtuzumab (Lemtrada)	12 mg/1.2 mL solution for infusion	Single-use vial	1,085.9258	12 mg/day IV for 5 days followed by 12 mg/day IV for 3 days after 12 months	Weekly average, Year 1: 1,249 Year 2: 749	Year 1: 65,156 Year 2: 39,093
Natalizumab (Tysabri)	300 mg/15 mL solution for infusion	Single-use vial	3,374.9900	300 mg IV every 4 weeks	844	43,875
Ocrelizumab (Ocrevus)	30 mg/10 mL solution for infusion	Single-use vial	8,150.0000	600 mg IV every 6 months	625	32,600

IM = intramuscular; MIU = million International Units; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis.

[a] Sponsor-submitted price.[2]

[b] Before the patient initiates the maintenance dose (2 mg once daily), the patient must complete a starter pack over five days (0.25 mg once on day 1 and day 2; 0.25 mg twice on day 3; 0.25 mg three times on day 4; 0.25 mg five times on day 5).

[c] CADTH submission review for cladribine.[19]

Source: Unit prices of medications are taken from the Ontario Drug Benefit Formulary[18] or the Ontario Formulary Exceptional Access Program[20] (accessed April 2020), and do not include prescription fees, costs of dose preparation, or injection administration. Annual period assumes 52.18 weeks or 365.25 days for all comparators.

Appendix 2: Additional Information

Table 6: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking "no"	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking "poor"	None		

Table 7: 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 3: Summary of Other Health Technology Assessment Reviews of Drug

Table 8: Other HTA Findings

	Institute for Clinical and Economic Review (May 2, 2019) [a]
Treatment	SPMS in adults aged ≥ 18 years
Price	$7,273.97 per package of 30 oral tablets (2 mg each) [b]
Similarities with CADTH submission	**Model structure** • A multi-state, cohort Markov model consisting of 9 EDSS-based health states was developed using a lifetime time horizon in Microsoft Excel • Each 1-year cycle, patients either transitioned to health states with higher EDSS scores, remained in the same state, had a relapse, or progressed to death **Data inputs** • Baseline distribution of patients across the 9 EDSS categories reflected EXPAND's baseline measures [c] • Risk of EDSS progression, relative risk of relapse, and discontinuation rate (year 1 and year 2) from the EXPAND study [c] • EDSS-specific mortality multipliers from the study by Pokorski et al. [d] **Assumptions** • Treatment efficacy did not wane over time • Adults who discontinued siponimod followed the natural history progression of disease and only received BSC thereafter
Differences with CADTH submission	**Model structure** • Patients' disease SPMS-related prognosis did not improve — i.e., patients did not transition to health states with lower EDSS scores **Data inputs** • Natural history data on the progression of patients between EDSS states were from the London, Ontario, cohort database [e,f] • Discontinuation rate of 3% per year during year 3 and thereafter • Utility estimates were from the published study by Hawton et al. [g] • Age- and sex-specific mortality rates were from the US life tables in the Human Mortality Database [h] • Cost estimates were based on the Healthcare Common Procedure Coding System, the Centers for Medicare & Medicaid Services 2018 Clinical Laboratory Fee Schedule,[e] and the Centers for Medicare & Medicaid Services 2018 Physician Fee Schedule [i] **Assumptions** • Treatment comparator was BSC and did not include interferons • Stopping rule at EDSS score 7 applied in subgroup with active SPMS and not in the overall SPMS population • Adverse events were not considered in the model and did not affect discontinuation rate • Health state utility in the EDSS 9 state was 0

	Institute for Clinical and Economic Review (May 2, 2019) [a]
Issues noted by the review group	• The sponsor-submitted MAIC had numerous limitations • Natural history data for adults with SPMS by EDSS state were from an older study and may not represent current populations with MS due to differences in diagnostic and treatment practices • EXPAND enrolled adults with SPMS with active and non-active disease while FDA-approved labelling was limited to adults with SPMS with relapsing disease
Results of analyses by the review group	**Base-case analysis of siponimod's ICER vs. BSC [a]** • Overall SPMS population, ICER = $1.15 million per QALY gained • Subgroup with relapses within 2 years of enrolment (i.e., adults with active SPMS), ICER = $433,000 **Scenario analyses** • Siponimod vs. interferon beta-1b (based on the sponsor-submitted MAIC), ICER = $2,110,000 per QALY gained • Subgroup with non-active disease, ICER for siponimod vs. BSC = $3,300,000 per QALY gained

BSC = best supportive care; EDSS = Kurtzke Expanded Disability Status Scale; HTA = Health Technology Assessment; ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; SPMS = secondary-progressive multiple sclerosis; QALY = quality-adjusted life-year; vs. = versus.

[a] The Institute for Clinical and Economic Review published an evidence report on the use of Mayzent to treat secondary-progressive multiple sclerosis [20]

[b] Sponsor's submission[21]

[c] Mayzent's product monograph[1]

[d] Published study[8]

[e] Centers for Medicare and Medicaid Services Clinical laboratory fee schedul[22]

[f] Published study[23]

[g] Published study[24]

[h] US Human mortality database [25]

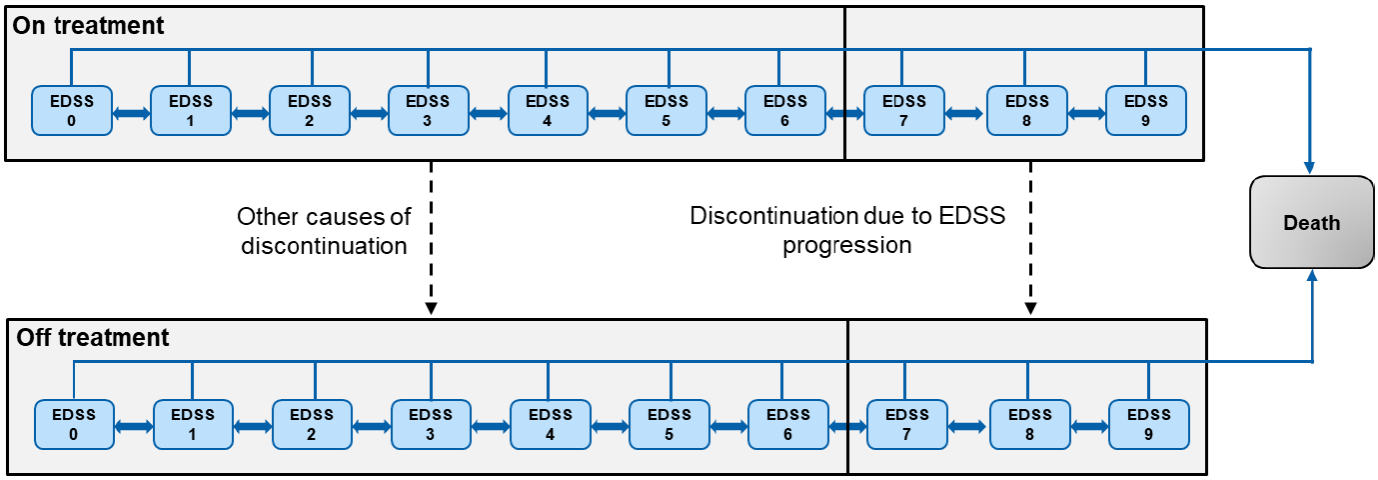
[h] Centers for Medicare and Medicaid Services. Physician fee schedule [26]

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

The sponsor developed a cohort multi-state Markov model to simulate the clinical course of disease progression through 10 health states, each defined according to an EDSS category (0 to 9).[2] The cohort comprised adults with SPMS who received treatment with siponimod, BSC, Extavia, Rebif, Avonex, or Betaseron. Cycle lengths were one year in duration. Each year, patients transitioned between EDSS states (higher or lower EDSS categories) or moved to the absorbing death state. Patients discontinued treatment when they achieved an EDSS score of 7 or greater while on treatment, as well as due to an annual incidence of other causes. Following discontinuation, patients switched to treatment with BSC.

Figure 1: Model Schematic — Cohort-Level Markov State-Transition Model



EDSS = Kurtzke Expanded Disability Status Scale.

Source: Sponsor-submitted pharmacoeconomic evaluation report.

Table 9: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Data from both the BSC and siponimod arms of the EXPAND trial.[a]	Appropriate
Efficacy	In patients taking BSC, transition probabilities between EDSS states and annualized relapse rates were derived from the placebo arm of the EXPAND clinical trial.[a,b] In those taking siponimod, Extavia, Rebif, Avonex, or Betaseron, the natural history data were adjusted by a relative treatment effect for both progression and relapse rates, which were derived from a sponsor-funded matching-adjusted indirect comparison.[c]	Based on CADTH's clinical review, the sponsor-submitted indirect treatment comparison had several limitations that threatened the internal and external validity of the findings. Such limitations stemmed from differences between the included studies' design, eligibility criteria, baseline characteristics of study populations, and outcomes assessment. See CADTH's Clinical Review Report for further details.
Natural history	Data on natural history, with respect to the progression of patients between EDSS states, the annualized relapse rate, and the mean duration of each relapse event, were derived from the EXPAND trial.[a]	Appropriate

Data input	Description of data source	Comment
Utilities	The model's utility values were based on EDSS category: • Utility values for EDSS states 3 to 7 were derived from the EXPAND trial.[a] However, the values adopted in the new submission differed from those employed in the original model. • Utility values for EDSS 0, 1, 2, 8, and 9 were derived from the study by Orme et al.[d] • Disutility for a relapse was derived from the EXPAND trial.[a] The source of disutility associated with specific adverse events was not reported.	The sponsor assumed utility values for EDSS 8 and EDSS 9 were –0.094 and –0.24, respectively, while that of EDSS 7 was 0.383. The decrease in utility value of 0.476 from EDSS 7 to EDSS 8 was not consistent with recent published estimates of this decrease in adults with SPMS (e.g., decline in utility from EDSS 7 to EDSS 8 of 0.376 and from EDSS 8 to EDSS 9 of 0.021)[k] and, therefore, lacked face validity. The values in the new submission favoured siponimod. As no explanation for the change was given, CADTH adopted the original values.
Adverse events (indicate which specific adverse events were considered in the model)	Data on the following adverse events were based on the EXPAND trial,[a] while the source for assuming different proportions of serious events vs. non-serious events was not reported. • Nasopharyngitis • Urinary tract infection • Fall • Hypertension • Fatigue • Upper respiratory tract infection • Dizziness • Nausea • Influenza • Diarrhea • Back pain • Alanine aminotransferase level increased • Pain in extremity • Arthralgia • Depression	Appropriate
Mortality	The probability of mortality was based on adjusting all-cause mortality data for the Canadian general population to provide a probability of death specific to each EDSS state.[e] Mortality associated with EDSS state was estimated by multipliers derived from the study by Pokorski et al.[f]	The use of hazard ratios of mortality associated with EDSS categories from Pokorski et al.[f], a study of patients with multiple sclerosis from 1972 to 1985, likely did not account for current disease management practices in Canada. Furthermore, CADTH's clinical expert suggested that any link between EDSS categories and mortality risk in the current population may be confounded by age.
Resource use and costs		
Drug	The cost of siponimod was the sponsor's submitted price,[b] while the costs of the comparators were from Ontario Drug Benefit's Exceptional Access Program.[g]	Appropriate
Administration	Drug administration (e.g., injection administration) and monitoring resources (e.g., neurology visits, ophthalmology visits) were based on the opinions of the sponsor's experts in Canada. Unit costs for such health	Appropriate

Data input	Description of data source	Comment
	services were from the Ontario Schedule of Benefits,[h] Ontario Schedule for Laboratory Fees,[i] and Ontario Case Costing Initiative.[j]	
Adverse events	Adverse event management costs were based on the ocrelizumab drug submission to the National Institute for Health and Care Excellence.[k] The report lacked full details.	Resource use and cost data in patients who had a different form of multiple sclerosis received a different intervention (infusion therapy) and whose disease management took place in a different clinical setting (UK) may have limited generalizability to such outcomes in adults with SPMS who received treatment with siponimod in Canada.
Health state	The sponsor assumed that the disease management costs associated with each EDSS category and relapse events were the same as in patients with RRMS based on the CADTH Therapeutic Review of treatments for RRMS.[d]	Resource use and cost data in patients who had a different form of multiple sclerosis may not accurately capture such outcomes in adults with SPMS.

BSC = best supportive care; EDSS = Kurtzke Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

[a] Mayzent's product monograph.[1]

[b] Sponsor's submission[2]

[c] CDR request for additional information regarding the Mayzent CDR review[3]

[d] CADTH therapeutic review[7]

[e] Published study[9]

[f] Published study[8]

[g] Ontario Ministry of Health and Long-Term Care's Exceptional access program[27]

[h] Ontario Ministry of Health and Long-Term Care's Schedule of benefits for physician services under the Health Insurance Act[13]

[i] Ontario Ministry of Health and Long-Term Care's Schedule of benefits for laboratory services[14]

[j] Published source[28]

[j] National Institute for Health and Care Excellence review of ocrelizumab for treating primary progressive multiple sclerosis[29]

[k] Published study[24]

Table 10: Sponsor's Key Assumptions

Assumption	Comment
BSC was not considered an appropriate comparator.	CADTH clinical reviewers suggested that the most relevant comparator was BSC based on the lack of consistent efficacy data for IFNs and the high proportion of patients who will have been treated with IFNs prior to development of SPMS.
Patients either progress to a higher EDSS state, remain in the same state, regress to a lower severity EDSS state, or die.	The clinical experts indicated the likelihood of transitioning to a lower level of disability (lower EDSS score) decreases with transitions to more severe EDSS levels, and that it is unlikely for patients' conditions to improve while they are receiving treatment.
Relapse severity for all comparators was the same as for siponimod.	Likely appropriate
Treatment efficacy did not wane over time.	Likely appropriate. The clinical expert felt that treatment waning is not a common phenomenon in patients with SPMS.
Adults with EDSS scores ≥ 7 discontinued from siponimod, or IFN, use and subsequently received BSC.	Likely appropriate

Assumption	Comment
Adults who discontinue siponimod follow the natural history progression of disease.	Appropriate since there is currently no data that supports extended treatment benefit with siponimod after a patient has discontinued
Utility decreases significantly in patients who progress from EDSS 7 to EDSS 8.	Not appropriate; lacks face validity and is inconsistent with observed estimates from a recent study of utility values in adults with SPMS
The relative hazard of mortality increases with the EDSS category.	CADTH's clinical experts suggested that any link between EDSS categories and mortality risk in the current population may be confounded by age.
Only a proportion of relapses required hospitalization.	Appropriate
Disease progression by EDSS level, mortality, relative treatment effect of siponimod vs. IFNs or natalizumab, treatment discontinuation rates, and health state utility values are not influenced by whether the adult has active SPMS.	Not appropriate; CADTH's clinical experts indicated that these variables would be influenced by whether the patient had active disease or not

BSC = best supportive care; EDSS = Kurtzke Expanded Disability Status Scale; IFN = interferon; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Table 11: Mortality Multipliers by EDSS Level

EDSS level	Sponsor submission	CADTH revised estimates
2	1.60	1.60
3	1.64	1.60
4	1.67	1.84
5	1.84	1.84
6	2.27	1.84
7	3.10	1.84
8	4.45	4.44
9	6.45	4.44

EDSS = Kurtzke Expanded Disability Status Scale.

Source: Sponsor-submitted pharmacoeconomic evaluation report, Sadovnick et al.

Table 12: Transition Probabilities Between EDSS Levels

From/to	0	1	2	3	4	5	6	7	8	9
	Sponsor submission									
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.0000	0.0000	0.5755	0.2791	0.1107	0.0271	0.0067	0.0002	0.0007	0.0000
3	0.0000	0.0000	0.0782	0.4286	0.3291	0.1184	0.0423	0.0015	0.0019	0.0000
4	0.0000	0.0000	0.0154	0.1631	0.4127	0.2506	0.1456	0.0066	0.0061	0.0000
5	0.0000	0.0000	0.0028	0.0448	0.1914	0.3099	0.4024	0.0257	0.0228	0.0002
6	0.0000	0.0000	0.0001	0.0027	0.0186	0.0676	0.7847	0.0773	0.0484	0.0005
7	0.0000	0.0000	0.0000	0.0004	0.0036	0.0185	0.3318	0.2903	0.3490	0.0064
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

From/to	0	1	2	3	4	5	6	7	8	9
	CADTH re-estimate									
From/to	0	1	2	3	4	5	6	7	8	9
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.0000	0.0000	0.5755	0.2791	0.1107	0.0271	0.0067	0.0002	0.0007	0.0000
3	0.0000	0.0000	0.0000	0.5068	0.3291	0.1184	0.0423	0.0015	0.0019	0.0000
4	0.0000	0.0000	0.0000	0.0000	0.5911	0.2506	0.1456	0.0066	0.0061	0.0000
5	0.0000	0.0000	0.0000	0.0000	0.0000	0.5489	0.4024	0.0257	0.0228	0.0002
6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8738	0.0773	0.0484	0.0005
7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.6446	0.3490	0.0064
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS = Kurtzke Expanded Disability Status Scale.

Source: Sponsor-submitted pharmacoeconomic evaluation report.

Table 13: Utility Values by EDSS Level

EDSS level	EXPAND regression-based estimates: Original model	Orme et al.[a]	Estimates used by sponsor: Revised model	Estimates employed by CADTH
2		0.66	0.66	0.66
3	0.644	0.529	0.647	0.644
4	0.611	0.565	0.623	0.611
5	0.583	0.473	0.594	0.583
6	0.548	0.413	0.554	0.548
7	0.420	0.252	0.383	0.420
8		–0.094	–0.094	0.074
9		–0.24	–0.24	–0.072

EDSS = Kurtzke Expanded Disability Status Scale.

Source: Sponsor-submitted pharmacoeconomic evaluation report, Orme et al.

[a] Utilities reported by EDSS level in a study by Orme et al.[7]

Table 14: CADTH Reanalyses — Summary

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. BSC
1. Allowance for no improvement, based on a reanalysis that excluded the probability of health status improvement					
BSC	696,323		3.43		
Siponimod	842,085	145,763	4.37	0.94	154,766
2. Published mortality multipliers, based on a reanalysis that included the published mortality multipliers					
BSC	634,960		5.80		
Siponimod	784,241	149,282	6.83	1.04	144,058

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. BSC
3. Revised utility values, based on a reanalysis that adopted revised utility values to ensure the disutility between states 7 and 8 and between states 8 and 9 reflected the data from Orme et al. and that the utility value for EDSS level 8 approximated the results of the EXPAND trial					
BSC	616,279		7.20		
Siponimod	765,560	149,281	8.01	0.81	184,811
4. Correcting the confidence interval of the relative relapse rate for siponimod vs. BSC					
BSC	613,375		5.77		
Siponimod	764,099	150,725	6.77	1.00	151,965

BSC = best supportive care; EDSS = Kurtzke Expanded Disability Status Scale; QALY = quality-adjusted life-year; vs. = versus.

Note: All costs are presented in 2019 Canadian dollars.

Source: Total costs and QALYs are based on a revised economic model submitted to CADTH on November 26, 2019.

Table 15: CADTH Base Case — Disaggregated Results

		BSC	Siponimod
Undiscounted	Drug acquisition costs	0	$185,577
	Drug administration and monitoring costs	0	$2,016
	Adverse event costs	0	$593
	Disease management costs	$851,490	$823,901
	Relapse costs	$45,501	$41,495
	TOTAL COSTS	$896,990	$1,053,582
	QALYs	6.09	7.00
	Life-years	25.15	25.52
Discounted	Drug acquisition costs	0	$173,174
	Drug administration and monitoring costs	0	$1,944
	Adverse event costs	0	$553
	Disease management costs	$681,141	$655,711
	Relapse costs	$36,745	$32,986
	TOTAL COSTS	$717,886	$864,310
	QALYs	5.41	6.17
	Life-years	20.68	20.94

BSC = best supportive care; QALY = quality-adjusted life-year.

Note: All costs are presented in 2019 Canadian dollars.

Source: Costs are based on a revised economic model submitted to CADTH on November 26, 2019, and are from the same Monte Carlo simulation as the results in Table 4.

Table 16: CADTH Scenario Analysis for All Patients With SPMS

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. BSC
BSC	685,955		5.39		
Siponimod	832,126	146,172	5.89	0.50	294,309

BSC = best supportive care; QALY = quality-adjusted life-year; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

Note: All costs are presented in 2019 Canadian dollars.

Source: Total costs and QALYs are based on a revised economic model submitted to CADTH on November 26, 2019, and are based on incorporating the corrections detailed earlier.[16]

Table 17: CADTH Scenario Analysis Applying a Treatment Waning Effect

	Total costs ($)	Incremental cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental cost ($) per QALY gained vs. BSC
BSC	719,261		5.40		
Siponimod	84,171	144,910	5.94	0.54	269,118

BSC = best supportive care; QALY = quality-adjusted life-year; vs. = versus.

Note: For this CADTH scenario analysis applying a treatment waning effect, full efficacy was for years 1 to 3 after treatment initiation. Partial efficacy (75%) was from years 4 to 5. Partial efficacy (50%) was from years 6 to 50. Total loss of efficacy was after 50 years. All costs are presented in 2019 Canadian dollars.

Source: Total costs and QALYs are based on a revised economic model submitted to CADTH on November 26, 2019, and are based on incorporating the corrections detailed earlier.[16]

References

1. Mayzent (siponimod tablets): film coated tablets, 0.25 mg and 2 mg siponimod (as siponimod fumaric acid), oral [product monog raph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2020 Feb 20.
2. Pharmacoeconomic evaluation. In: CDR submission: Mayzent (siponimod), 0.25 mg and 2 mg film-coated oral tablets) [**CONFIDENTIAL** sponsor's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2019 Oct 8.
3. Novartis response to October 8 2019 CDR request for additional information regarding the Mayzent CDR review [**CONFIDENTIAL** additional sponsor's information]. Dorval (QC): Novartis; 2019 Oct 8.
4. Pharmacoeconomic evaluation. In: CDR submission: Mayzent (siponimod), 0.25 mg and 2 mg film-coated oral tablets) [**CONFIDENTIAL** sponsor's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2020, February 7th.
5. Clinical Study Report: CBAF312A2304. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312 [**CONFIDENTIAL** internal sponsor's report]. Basel (CH): Novartis Pharmaceutical Company; 2014 Jan 20.
6. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis. *(CADTH therapeutic review vol.1, no 2b)*. Ottawa (ON): CADTH; 2014: https://www.cadth.ca/media/pdf/TR0004_RRMS_ScienceReport_e.pdf. Accessed 2020 Jan 9.
7. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of peop le with multiple sclerosis in the UK. *Value Health.* 2007;10(1):54-60.
8. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med.* 1997;29(2):101-106.
9. Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. *Neurology.* 1992;42(5):991-994.
10. Novartis response to December 3 2019 CDR request for additional information regarding the Mayzent CDR review [**CONFIDENTIAL** additional sponsor's information]. Dorval (QC): Novartis; 2019 December 5.
11. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol.* 2018;17(5):405-415.
12. Statistics Canada. Table: 13-10-0392-01.Deaths and age-specific mortality rates, by selected grouped causes. 2019; https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039201. Accessed 2020 Jan 9.
13. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective March 1, 2016. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20160401.pdf. Accessed 2020 Jan 9.
14. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for laboratory services. Toronto (ON): The Ministry of Health and Long-Term Care; 2020 Jan 1: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn2020.pdf. Accessed 2020 Jan 9.
15. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2017 Dec 20.
16. Novartis response to November 19 2019 CDR request for additional information regarding the Mayzent CDR review [**CONFIDENTIAL** additional sponsor's information]. Dorval (QC): Novartis; 2019 Nov 26.
17. Novartis response to March 20 2020 CDR request for additional information regarding the Mayzent CDR review [**CONFIDENTIAL** additional sponsor's information]. Dorval (QC): Novartis; 2020 Mar 25.
18. Ontario Ministry of Health Long-Term C. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 Apr 15.
19. CADTH Common Drug Review pharmacoeconomic review report: cladribine (Mavenclad- EMD Serono). Ottawa (ON): CADTH; 2018 Oct https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0546_Mavenclad_PE_Report.pdf. Accessed 2020 Apr 28.
20. Siponimod for the treatment of secondary progressive multiple sclerosis: effectiveness and value. Boston (MA): Institute for Clinical and Economic Review; 2019 Jun 20: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Final_Evidence_Report_062019.pdf. Accessed 2020 Jan 9.
21. IBM Micromedex Red Book. 2019; https://www.ibm.com/products/micromedex-red-book. Accessed 2019 Apr 18.
22. Centers for Medicare and Medicaid Services. Clinical laboratory fee schedule. 2018; https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html. Accessed 2018 Nov 20.
23. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis, a geographically based study 10: re lapses and long-term disability. *Brain.* 2010;133(7):1914-1929.
24. Hawton A, Green C. Health utilities for multiple sclerosis. *Value Health.* 2016;19(4):460-468.
25. The Human mortality database: U.S.A. specific tables. https://www.mortality.org/. Accessed 2019 Jan 14.
26. Centers for Medicare and Medicaid Services. Physician fee schedule. 2018; https://www.cms.gov/apps/physician-fee-schedule/overview.aspx.. Accessed 2018 Nov 20.

27. Ontario Ministry of Health and Long-Term Care. Exceptional access program. 2019; http://health.gov.on.ca/en/pro/programs/drugs/eap_mn.aspx. Accessed 2020 Jan 9.

28. Health Data Branch. Staging-health data branch web portal. 2016; https://stage.hsim.health.gov.on.ca/hdbportal/?destination=front_page. Accessed 2017 Dec 20.

29. National Institute for Health and Care Excellence. Ocrelizumab for treating primary progressive multiple sclerosis [ID938]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10153/documents. Accessed 2018 Jul.